CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218527Orig1s000

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA 505(b)(2)
Application Number(s)	218527
Priority or Standard	Standard
Submit Date(s)	August 30, 2023
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Office/Division	ORDPURM/ DUOG
Reviewer Name(s)	Roger Wiederhorn MD, Medical Officer Mark Hirsch MD, Medical Officer Team Leader
Established/Proper Name	Tadalafil Chewable Tablets
(Proposed) Trade Name	pending
Applicant	NOVITIUM Pharma
Dosage Form(s)	Chewable Tablets 5 mg, 10 mg, 20 mg
Applicant Proposed Dosing Regimen(s)	• Erectile dysfunction (ED) for use as needed prior to sexual activity • Signs and symptoms of benign prostatic hyperplasia (BPH), taken at approximately the same time of day. • Coexisting ED and BPH, taken at approximately the same time every day.
Applicant Proposed Indication(s)/Population(s)	ED BPH
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s)	Men with ED Men with BPH Men with ED and BPH

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity

OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

Tadalafil is a selective phosphodiesterase type 5 inhibitor (PDE5i). Tadalafil was first approved for marketing, November 21, 2003, under the tradename Cialis, for the treatment of ED as needed once daily. On January 7, 2008, Cialis was approved for once-daily use at a dose of 2.5 mg (with an increase to 5 mg if required) for the treatment of ED. Cialis was approved on October 6, 2011, for the treatment of the signs and symptoms of BPH, and for the treatment of coexisting ED and BPH, each at a dose of 5 mg once-daily. On October 10, 2013, tadalafil was approved for co-administration with finasteride in the treatment of BPH with a recommended 26-week duration of concomitant treatment.

Currently, tadalafil it is indicated for the treatment of (i) erectile dysfunction (ED), for use as needed prior to sexual activity and for once daily use; (ii) signs and symptoms of benign prostatic hyperplasia (BPH), taken at approximately the same time every day; and (iii) coexisting ED and BPH, taken at approximately the same time every day. The dose strengths for the treatment of these conditions are 2.5 mg, 5 mg, 10 mg, and 20 mg. The 2.5 mg dosage form of Cialis is indicated solely for the treatment of ED for once daily use without regard to timing of sexual activity.

Tadalafil is also available in oral tablet (as Adcirca) and suspension dosage forms (as Tadliq) for the treatment of pulmonary arterial hypertension (WHO Group I) to improve exercise ability. This Applicant did not request inclusion of this PAH indication in labeling for this NDA.

Sponsor has submitted an NDA for Tadalafil Chewable Tablets which is a new dose formulation. The proposed to-be-marketed dosage strengths for Tadalafil Chewable Tablets are 5 mg, 10 mg and 20 mg, for the indications of (i) erectile dysfunction (ED), for use as needed prior to sexual activity; (ii) signs and symptoms of benign prostatic hyperplasia (BPH), taken at approximately the same time every day; and (iii) coexisting ED and BPH, taken at approximately the same time every day.

The NDA is supported by two comparative bioavailability and safety studies (TADA-22-008 and TADA-22-051) of the Sponsor's Tadalafil Chewable Tablets (Fasted) vs. the Listed Drug (LD), Cialis Tablets (Fasted) pursuant to section 505(b)(2) of the Federal Food, Drug and Cosmetic Act (FDCA).

1.2. Conclusions on the Substantial Evidence of Effectiveness

We conclude that the NDA application contains substantial evidence that the drug is effective for its intended use with the results of studies TADA-22-051, TADA-22-008 and TADA-23-023 showing comparable bioavailability of Tadalafil Chewable Tablets 20 mg and Cialis 20 mg in the fed, fasted states and with and without water in the fasted state.

1.3. Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Integrated Assessment

No new safety signals emerged from the relative bioavailability studies. Based on substantial evidence of effectiveness and no new safety signals, we conclude that the benefit-risk assessment is acceptable for Tadalafil Chewable Tablets.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Cialis is approved for the treatment of: • Erectile Dysfunction • Benign Prostatic Hypertrophy The evidence for effectiveness is provided by the Referenced Drug, Cialis.	Cialis, the reference drug for this 505(b)(2) application, is approved for the treatment of male erectile dysfunction (ED) and benign prostatic hypertrophy (BPH). ED is the inability to achieve an erection suitable for vaginal penetration and of duration sufficient to complete sexual intercourse. Cialis improves these two capabilities. ED can cause lowered self-esteem and interpersonal difficulty. BPH is the benign enlargement of the prostate so that it obstructs the urethral flow of urine. This could result in symptoms of inadequate bladder emptying, frequent urination, nocturia, straining to urinate and urgency. Urinary tract infections and bladder calculi can also be caused by BPH. Tadalafil relaxes the smooth muscle component of BPH allowing

Dimension	Evidence and Uncertainties	Conclusions and Reasons
		the flow urine and other symptoms to improve. Prostatic obstruction can progress to urinary retention, hydronephrosis and renal damage. Urinary tract infections can progress to sepsis which can be life-threatening.
Current Treatment Options	Current treatment options for ED include: • Phosphodiesterase 5 inhibitors • Eroxin Topical Gel • Intracavernosal injections of pharmacologic agents causing erections • Intra-urethral prostaglandin • Penile surgical insertion of protheses Current treatment options for BPH treatment include: • Tadalafil, phosphodiesterase 5 inhibitor • Finasteride and Dutasteride both 5-alpha reductase inhibitors • Tamsulosin, an alpha blocker • Open surgery or transurethral resection of the prostate • Laser or temperature treatment of the prostate • Urolift or mechanical device separation the obstructing prostate lateral lobes.	The benefit of this product is that it can be administered with or without water. While it does require the ability to chew, it may be advantageous for patients who cannot easily swallow pills. Product is anticipated to have the same risk benefit profile as Cialis, the reference product.
Benefit	• The advantage of Tadalafil Chewable Tablets is that in some patients this product may be easier to swallow.	Useful for patients who have difficulty swallowing tablets

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• No subject reported difficulty swallowing or choking. • No oro-mucosal irritation was observed. • No new clinical safety signals were observed. • Laboratory abnormalities observed, including increased transaminases and decreased hemoglobin, were considered to be a consequence of baseline lab abnormalities, lab results variability, study design issues, and other factors.	Risks are the same as the reference product as is the risk management.

1.4. Patient Experience Data

This is a 505 (b)(2) application. Patient experience is provided by the experience for the reference drug,

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include: **This application is a 505 (b)(2) application. The submission consists of 3 bioeqivalence studies TADA-21-079, TADA-22-008 and TADA-22-051 and one bioavailabilty study TADA-23-023.**	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as:	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
X	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

This Sponsor has developed an oral chewable tablet containing tadalafil. This Sponsor purports that the new chewable tablet can be taken with or without the need for water to reach the GI tract and to attain bioequivalent tadalafil PK results to the reference product under the tradename CIALIS. The Sponsor asserts that the product (referred to in this review as Tadalafil Chewable Tablets) provides an alternative to CIALIS tablets in the treatment of ED. Tadalafil Chewable Tablets has been developed in three dose strengths: 5 mg, 10 mg, 10 mg.

The product is a round-shaped, mottled blue-colored, biconvex tablet supplied as 5 mg, 10 mg, and 20mg dose strengths.

CIALIS is an approved drug for the treatment of ED, BPH and BPH/ED. The Sponsor is applying for 505(b)(2) approval referencing CIALIS NDA 21-368. Below are the submissions and approval dates for the submissions to NDA 21-368:

- NDA 21-368 SEQ 001 submitted June 29, 2001, and approved November 21, 2003, for prn use for ED.
- NDA 21-368 SE-011 submitted December 21, 2007, and approved January 7, 2008, for once daily use for ED.
- NDA 21-368 SEI-20 submitted December 6, 2010, and approved October 6, 2011, for once daily use to treat BPH.
- NDA 21-363 SEI-21 submitted December 6, 2010, and approved October 6, 2011, for once daily use to treat ED/BPH.

These submissions and the resulting CIALIS product labeling provide the therapeutic context for Tadalafil Chewable Tablets. The reader may refer to the submissions listed above as references. This Sponsor has access to approved labeling as the basis of their 505(b)(2) application. The proposed prescription labeling incorporates results of the submissions above by reference, additional studies conducted by the CIALIS sponsor, and relevant additional safety findings obtained throughout CIALIS marketing cycle.

2.2. Analysis of Current Treatment Options

The tables below show the currently available PDE5 inhibitors for the treatment of erectile dysfunction (ED) and medication treatments for benign prostatic hyperplasia (BPH).

Table 1: Currently Available PDE5 Inhibitors for the Treatment of Erectile Dysfunction (ED)

	VIAGRA (sildenafil)	CIALIS (tadalafil)	LEVITRA (vardenafil)	STAXYN (vardenafil ODT)	STENDRA (avanafil)
Manufacturer	Pfizer	Eli Lilly	Bayer	Bayer	Vivus
Date Introduced	March 1998	Feb 2003	April 2003	June 2010	April 2012
Dosage	50mg,100mg	2.5 mg, 5mg, 10mg, 20mg	2.5 mg, 5mg, 10mg, 20mg	oral dispersible tablet (ODT), 10 mg	50 mg. 100 mg, 200 mg

Source: Reviewer table derived from Up to Date: PDE5i Treatment of ED: Literature review August 2023, Topic update July 17, 2023.

Table 2: Currently Available Oral Drug Treatments for BPH

Medications	Regimen	Advantages	Disadvantages/AEs
Phosphodiesterase -5 inhibitor, tadalafil	Daily oral dosing	Decreases lower urinary tract symptoms (LUTS)	Headaches, dyspepsia, back pain, myalgias, flushing, limb pain
Alpha-Adrenergic Antagonists specific and non-specific for the α1 receptor	Daily oral dosing	Decreases lower urinary tract symptoms (LUTS)	Dizziness, hypotension, ejaculatory dysfunction
5-Alpha Reductase Inhibitors	Daily oral dosing	Decreases LUTS, Reduces the risk of urinary retention and need for BPH-related surgery	Less effective in smaller prostates, impotence, decreased libido loss, ejaculatory dysfunction, gynecomastia, may increase risk of higher grade prostate cancer
Combination Therapy Alpha-Adrenergic Antagonists and 5-Alpha Reductase Inhibitors	Daily oral dosing	Superior results over monotherapy	Impotence, decreased libido, ejaculatory dysfunction, gynecomastia, may increase risk of higher grade prostate cancer

Source: Reviewer table derived from Up to Date: Medical Treatment of Benign Prostatic Hyperplasia (BPH): Literature review August 2023, Topic update July 31, 2023.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The Sponsor provided a summary of US regulatory actions and marketing history of tadalafil on page 5 of their Clinical Summary as follows:

"Tadalafil is marketed as an oral tablet dosage form in strengths of 2.5 mg, 5 mg, 10 mg and 20 mg under the brand name Cialis® by Eli Lilly and Co (NDA 021368). Tadalafil (5 mg), in combination with the 5α-reductase inhibitor, finasteride (5 mg), is also available for short-term (26 weeks) initiation of treatment for BPH as an oral capsule dosage form from Veru Inc. (Entadfi®; NDA 215423). The 2.5 mg dosage form of Cialis is indicated solely for the treatment of ED for once daily use without regard to timing of sexual activity.

Tadalafil is also available in oral tablet and oral suspension dosage forms for the treatment of pulmonary arterial hypertension (PAH - WHO Group I) to improve exercise ability, from Eli Lilly (Adcirca®, NDA #022332) and CMP Development, LLC (Tadliq®, NDA #214522), respectively.

Reviewer's Comment: The once daily use indication and the PAH indication were not proposed as part of this Sponsor's NDA submission.

Cialis was first approved on 11/21/2003 for the treatment of ED as needed prior to sexual activity as tablets in doses of 5 mg, 10 mg and 20 mg. On 01/7/2008, Cialis was approved for once-daily use at a dose of 2.5 mg (with an increase to 5 mg if required) for the treatment of ED (NDA SUPPL-11). Cialis was approved on 10/6/2011 for the treatment of the signs and symptoms of BPH (NDA SUPPL-20), and the treatment of coexisting ED and BPH (NDA SUPPL-21), each at a dose of 5 mg once-daily. A "Prior Approval" supplement (NDA SUPPL- 22) provided for co-administration with finasteride in the treatment of BPH with a recommended 26-week duration of concomitant therapy on 10/10/2013.

Since its approval, Cialis has undergone multiple label changes for safety, most notably the inclusion of: (i) increased risk of non-arteritic ischemic optic neuropathy (NAION) on 04/29/2014 (SUPPL-23); (ii) increased risk of hypotension from concomitant use with guanylate cyclase stimulators such as riociguat; (iii) risk of peripheral edema and diarrhea in the elderly on 04/22/2016 (SUPPL-27); and (iv) an approximate 2-fold increase in the risk of NAION, on 05/05/2017 (SUPPL-29).

Since the introduction of Cialis, 38 generic dosage forms of tadalafil tablets have been approved (including 5 subsequently discontinued products). The first generic dosage form was approved on 05/22/2018 (ANDA 090141, Teva Pharmaceuticals USA, Inc). The

most recent generic dosage form was approved on 03/03/2023 (ANDA 215949, Novitium Pharma). (b) (4)

3.2. Summary of Presubmission/Submission Regulatory Activity

- On July 25, 2022, DUOG provided Type B Pre-IND (PIND 162564) Meeting Written Responses: Various chemical and manufacturing process questions and issues were answered. Nonclinical comments included that oral safety studies may be required if safety signals are identified in humans that require further assessment. Sponsor was also asked to provide information on the qualitative and quantitative composition and acceptable daily intake levels for bubblegum flavor to support its safe use in the proposed chewable dosage form product. Clinical and Clinical Pharmacology recommended earlier PK time points in the bioequivalence studies and more frequent vital sign timepoints during the planned studies. Oral mucosal assessment is to be performed during bioequivalence studies. A PK Study to assess use of water vs. no water was suggested. The Sponsor's planned fed fasted and fasted bioequivalence studies were acceptable. The Sponsor will provide an ISS but also adverse event data from the bioavailability studies. The Sponsor is to provide safeguards for misuse by children in light of bubble gum flavoring.
- On November 18, 2022, the planned Phase 1 studies for IND 162564 were deemed safe to proceed.
- On April 4, 2023, the Pediatric Review Committee (PeRC) confirmed that the Tadalafil Chewable Tablets iPSP was appropriate for a full waiver.
- On August 30, 2023, NDA 218527 was submitted.

3.3. Foreign Regulatory Actions and Marketing History

Not applicable.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The Office of Study Integrity and Surveillance (OSIS) concluded that the clinical and bioanalytical sites at which the pivotal comparative bioavailability (BA) studies (TADA-22-051 and TADA-23-023) were conducted were Acceptable.

4.2. Product Quality

In their Integrated Quality Assessment dated May 12, 2024, Office of Pharmaceutical Quality

(OPQ) recommended Approval of this NDA. OPQ summarized as follows:

- The product contains 5 or 10 mg of tadalafil as the active ingredient, The inactive ingredients are: colloidal silicon dioxide, croscarmellose sodium, FD&C blue No. 1 aluminum lake, hydroxypropyl cellulose, lactose monohydrate, magnesium stearate, mannitol, microcrystalline cellulose, sodium lauryl sulfate, sucralose and bubblegum flavor (acacia, artificial and natural flavors).
- All the excipients are within the FDA IID limits of previously approved oral drug products. There are no novel excipients in the drug product formulation.
- The submitted CMC information is sufficient to assure the identity, strength, purity and quality of the drug substance and drug product.
- The overall OPMA recommendation on manufacturing facilities is Adequate.
- The request for categorical exclusion from preparation of an environmental assessment is granted.
- The expiration dating period is 24 months
- Multiple requests for tradename have been denied by FDA. For this reason, this application will be approved without the drug product tradename.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

In their final Pharmacology/Toxicology review dated April 24, 2024, PharmTox concluded that the available data support Approval. No additional nonclinical studies were needed to support NDA approval. There were no notable nonclinical pharmacology or toxicology issues identified and labeling was acceptable.

4.5. Clinical Pharmacology

In their Office of Clinical Pharmacology Review dated May 24, 2024, Clinical Pharmacology concluded that application was Acceptable for Approval from the Clinical Pharmacology perspective. Clinical Pharmacology confirmed that the requirement for bioequivalence comparing Tadalafil Chewable Tablets and Cialis 20 mg tablets had been met. Food and water intake had no significant effect. The noted delay in Tmax with food was not clinically meaningful. The noted longer half-lives were not of clinical consequence and labeling was determined to be acceptable.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 3 : Clinical Trials Relevant to this NDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	Centers Countries
TADA-21-079-	A SINGLE-DOSE, OPEN-LABEL, RANDOMIZED, BALANCED, THREE-PERIOD, TWO-TREATMENT, THREE-SEQUENCE, CROSSOVER STUDY IN HEALTHY ADULT MALE SUBJECTS TO ASSESS RELATIVE ORAL BIOAVAILABILITY AND EFFECT OF FOOD ON TEST FORMULATION OF TADALAFIL CHEWABLE TABLETS 20 MG UNDER FED (TREATMENT A) AND FASTING (TREATMENT B) CONDITIONS WITH A REFERENCE FORMULATION OF CIALIS® (TADALAFIL) 20 MG TABLETS (TREATMENT C) UNDER FASTING CONDITIONS.	Single doses of Tadalafil 20mg Chewable Tablets (Treatments A[fed] and B [fasted]) and Cialis 20mg (Treatment C [fasted]). 12-day interval between doses	Evaluate relative bioavailability of A vs B and B vs C. Cmax and AUC least squared means were endpoints using 80-125% acceptance criteria	For subjects completing all three dosing regimens, duration was 29 days.	18 subjects enrolled 16 subjects completed the study	Healthy adult males	1 center India
TADA22-008-	AN OPEN-LABEL, BALANCED, RANDOMIZED, SINGLE-DOSE, TWO-TREATMENT, TWO-SEQUENCE, TWO-PERIOD, TWO-WAY CROSSOVER, RELATIVE ORAL BIOAVAILABILITY STUDY OF TADALAFIL CHEWABLE TABLETS 20 MG (T), WITH CIALIS® (TADALAFIL) TABLETS	In fasting subjects, a single dose of Tadalafil 20mg Chewable Tablets or Reference product Cialis 20mg	Evaluate relative bioavailability of test vs reference Cmax and AUC least squared means were endpoints using 80-125%	For subjects completing the study, duration was 19 days	14 subjects enrolled 13 subjects completed the study	Healthy adult males	1 center India

	20 MG (R) IN HEALTHY ADULT MALE SUBJECTS UNDER FASTING CONDITIONS.	12-day interval between doses	acceptance criteria				
TADA-22-051	A SINGLE-DOSE, OPEN-LABEL, RANDOMIZED, BALANCED, THREE-PERIOD, TWO-TREATMENT, THREE-SEQUENCE, CROSSOVER STUDY IN HEALTHY ADULT MALE SUBJECTS TO ASSESS THE RELATIVE ORAL BIOAVAILABILITY AND EFFECT OF FOOD ON TEST FORMULATION OF TADALAFIL CHEWABLE TABLETS 20 MG UNDER FED (TREATMENT A) AND FASTING (TREATMENT B) CONDITIONS WITH A REFERENCE FORMULATION OF CIALIS® (TADALAFIL) TABLETS 20 MG (TREATMENT C) UNDER FASTING CONDITIONS.	A single dose of Tadalafil 20mg Chewable Tablets (Treatments A[fed] and B [fasted]) and Cialis 20mg (Treatment C [fasted]). 14-day interval between doses.	Evaluate relative bioavailability of A vs B and B vs C. Cmax and AUC least squared means were endpoints using 80-125% acceptance criteria	For subjects completing all three dosing regimens, duration was 35 days	42 subjects enrolled 37 subjects completed study	Healthy adult males	1 center India
TADA-23-023	A SINGLE-DOSE, OPEN-LABEL, RANDOMIZED, BALANCED, TWO-PERIOD, ONETREATMENT, TWO-SEQUENCE, CROSSOVER STUDY TO ASSESS THE RELATIVE ORAL BIOAVAILABILITY OF TEST FORMULATION TADALAFIL CHEWABLE TABLETS 20 MG ADMINISTERED WITHOUT WATER (TREATMENT A) COMPARED	In fasting subjects, a single dose of Tadalafil Chewable Tablets administered with and without water	Evaluate relative bioavailability of Tadalafil Chewable Tablets with and without water. Cmax and AUC least squared means were	For subjects completing both study arms, duration was 21 days.	24 subjects enrolled 21 subjects completed study	Healthy adult males	1 center India

	WITH TADALAFIL CHEWABLE TABLETS 20 MG ADMINISTERED WITH WATER (TREATMENT B) IN HEALTHY ADULT MALE SUBJECTS UNDER FASTING CONDITIONS.	14-day interval between doses.	endpoints using 80-125% acceptance criteria				

5.2. Review Strategy

The clinical trials relevant to this NDA are listed in Table 3. Pilot Study TADA-21-079 used an initial formulation and did not document bioequivalence between CIALIS 20 mg and Tadalafil Chewable Tablets 20 mg. Studies TADA-22-008, TADA-22-051 and TADA-23-023 used a reformulated product and demonstrated various aspects of bioequivalence. Key aspects of study design and pharmacokinetic (PK) results are provided in the Efficacy section of this review. All available safety data are reviewed in detail in the Safety section of this review.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study TADA-21-079

6.1.1. Study Design

Overview and Objective

TADA-21-079: A SINGLE-DOSE, OPEN-LABEL, RANDOMIZED, BALANCED, THREE-PERIOD, TWO-TREATMENT, THREE-SEQUENCE, CROSSOVER STUDY IN HEALTHY ADULT MALE SUBJECTS TO ASSESS RELATIVE ORAL BIOAVAILABILITY AND EFFECT OF FOOD ON TEST FORMULATION OF TADALAFIL CHEWABLE TABLETS 20 MG UNDER FED (TREATMENT A) AND FASTING (TREATMENT B) CONDITIONS WITH A REFERENCE FORMULATION OF CIALIS® (TADALAFIL) 20 MG TABLETS (TREATMENT C) UNDER FASTING CONDITIONS.

Trial Design

This was a single-dose, open-label, randomized, balanced, three-period, two-treatment, three sequence, crossover study in healthy adult male subjects to assess oral bioavailability and food effect under fed and fasted conditions of *an initial formulation* of Tadalafil Chewable Tablets. The 20 mg tadalafil dose was tested as Tadalafil Chewable Tablets 20 mg vs. CIALIS Tablets 20 mg for the three study periods: Tadalafil Chewable Tablets 20 mg fed (Treatment A), Tadalafil Chewable Tablets 20 mg fasted (Treatment B), and CIALIS Tablets 20 mg fasted (Treatment C).

Table 4: TADA-21-079 Design Overview

Study Type	Study ID	Objectives	Design	Regime Route	N
BA BE	TADA-21-079	*BE* Tadalafil Chewable Tablets (Fasted [T] vs. Cialis (Fasted [R]) *Food Effect* Tadalafil Chewable Tablets (Fed [T] vs. Tadalafil Chewable Tablets (Fasted [T])	SD, 3-way, X-over T (Fed [A]) T (Fasted [B]) R (Fasted [C]) 0-72 hr PK 24 samples	Tadalafil Chewable Tablets, Fasted, 20 mg, Oral, Chewed Tadalafil Chewable Tablets, Fed, 20 mg, Oral, Chewed Cialis Tablets, Fasted, 20 mg, Oral	Enrolled: 18 Males 18 Dosed: Period 1: 18 Period 2: 18 Period 3: 16 B vs. C: 17 A vs. B: 15
Note: This study failed to show bioequivalence and drug product was reformulated for subsequent clinical studies					

Source: Table 10 of Clinical Summary in current submission

Eighteen (18) healthy male subjects were enrolled, and 16 subjects completed the study.

Primary Objectives:

- To assess the relative oral bioavailability of Tadalafil Chewable Tablets 20 mg (Treatment B) with Cialis (Tadalafil) 20 mg Tablets (Treatment C) in healthy adult male subjects under fasting conditions.

- To assess the effect of food on the oral bioavailability of single dose Tadalafil Chewable Tablets 20 mg (Treatment A vs. Treatment B) in healthy adult male subjects under fed and fasting conditions.

Secondary Objective:

- To monitor the safety and tolerability of single doses of investigational product when administered in healthy adult male subjects under fasting and fed conditions.

Table 5: Overall Investigational Plan TADA--21-079

Study Design	Single-dose, open-label, randomized, balanced, three-period, two-treatment, three-sequence, crossover study in healthy adult male subjects to assess oral bioavailability and food effect of

	Tadalafil Chewable Tablets 20 mg under fed and fasting conditions.
No. of Subjects	18
Housing	Subjects were housed in the clinic from at least 11.00 hours prior to dosing to at least 48.00 hours post-dose in each period.
Treatment Studied	A single dose of Tadalafil Chewable Tablets 20 mg under Fed (Treatment A) and Fasting (Treatment B) conditions and a single dose of Cialis (Tadalafil) Tablets 20 mg (Treatment C) under Fasting conditions, when administered to subjects in a sitting posture with 240 mL of water.
Blood Sampling	Pre-dose (00.00 hour) and 00.17, 00.25, 00.33, 00.50, 00.75, 01.00, 01.33, 01.67, 02.00, 02.33, 02.67, 03.00, 03.50, 04.00, 04.50, 05.00, 06.00, 08.00, 12.00, 16.00, 24.00, 48.00 and 72.00 hours of post-dose in each period. The 72.00 hour sample was collected on an ambulatory basis.
Treatment Sequence	The order of investigational products assignment for each subject was determined according to the randomization schedule. Subjects were randomized to one of the two sequences: either ABC, BCA, or CAB
Washout Period	The interval between doses was 12 days.

Source: Overall Study Design and Plan Description, page 38, CSR TADA-21-079

Subjects were included in study based upon the following, in brief, significant criteria:

1. Healthy adult male volunteers aged between 18-45 years of age with a Body Mass Index (BMI) between 18.5 kg/m² and 30.0 kg/m²
2. Non-smoker
3. Good health as determined by 12-lead ECG, X-ray, and clinical laboratory assessments.
4. Systolic blood pressure >=90 to <=140 mm Hg and diastolic blood pressure between >=60 to <=90 mm Hg at screening.

Subjects were excluded based upon the following, in brief, significant criteria:

1. Evidence of allergy or hypersensitivity to tadalafil.
2. Significant history or presence of asthma, urticaria, diabetes, migraine, hypertension, cardiovascular, pulmonary, neurological or psychiatric disease/disorder.
3. History or presence of significant dermatological, endocrine, immunological, hepatic, renal, hematopoietic, gastrointestinal, ongoing infectious diseases, or other significant diseases in the opinion of the physician.
4. History or evidence of exfoliative dermatitis, Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)

5. Subjects with hepatic encephalopathy, cholestasis, myasthenia, pre-existing liver disease, alcohol abuse and recent or active existing tinnitus
6. History of drug abuse within 3 months
7. History of difficulty swallowing
8. Any blood donation/excess blood loss with 90 days of period 1.
9. Consumption of caffeine and xanthene-containing products and tobacco-containing foods for at least 48 hours prior to check-in and throughout study.
10. Consumption of alcohol and its products, grapefruit and/or its juice and poppy containing foods within 72 hours prior to check-in and throughout the study.
11. Use of any prescribed medication within 14 days and any over-the -counter medicinal products within 7 days prior to check-in and throughout the study.
12. Myocardial infarction within the last 90 days.
13. Unstable angina or angina occurring during sexual intercourse.
14. Congestive heart failure within the past 6 months.
15. Uncontrolled arrythmias, hypotension (100/60 mm Hg) or hypertension (>140/90 mm Hg)
16. Stroke within the last 6 months
17. Symptoms of COVOD-19 or a positive COVID-19 test within the past 30 days
18. Any vaccination within the past 14 days.

Study Endpoints

The study endpoints where the typical pharmacokinetic parameters used to assess bioequivalence.

- The 90% CI of the relative geometric mean of the Test (Treatment B) to Reference (Treatment C) formulation for Ln-transformed Cmax and AUC 0-72 should be within 80.00% to 125.00% to establish bioequivalence under fasting conditions.

- The 90% CI of the relative geometric mean of the fed (Treatment A) and fasted (Treatment B) Test treatments for Ln-transformed Cmax and AUC 0-72 should be within 80.00% to 125.00% to establish absence of food effect on bioavailability.

Statistical Analysis Plan

See Study Endpoints section.

Protocol Amendments

The protocol was amended on October 22, 2021, with submission of a standardized meal plan.

6.1.2. Study Results

Compliance with Good Clinical Practices

See the Clinical Pharmacology review.

Financial Disclosure

The Sponsor provided financial disclosure for this NDA submission. A total of 3 investigators participated and none had a financial disclosure.

Patient Disposition

Overall, the study was conducted with 18 male subjects. 18 subjects were dosed in Period 1 and Period 2. 16 subjects were dosed in Period 3. Subjects (b) (6) were discontinued from study for Period 3 and not replaced.

16 subjects completed the Test Fed Treatment (A), 17 subjects completed the Test Fasted Treatment (B) and 18 subjects completed the Reference Fasted Treatment (C).

Protocol Violations/Deviations

Two subjects (b) (6) had blood samples drawn 5 minutes and 4 minutes later than scheduled (total 2 occasions).

There were 49 missing blood samples during the study. 48 of those samples were from Subjects (b) (6) who failed to report for Period 3 (24 samples each) and subject (b) (6) also failed to report for the ambulatory blood sample (1 sample) in period 2 of protocol.

Demographic Characteristics

The table below provides a listing of the individual patient demographics in this study.

Table 6: Individual and Mean Demographic Data of Subjects Enrolled in Study TADA-21-079

Sub. No.	Age (years)	Height (cm)	Weight (kg)	BMI (Kg/m²)	Race
(b) (4)					
Min	22	155	53	18.91	
Max	44	181	90	29.74	
Mean	35.3	169.2	71.7	25.567	
SD	5.44	6.32	11.68	3.7390	

Source: Table 01 in Study Appendix 16.2.4

A review of the case report forms (CRFs) for this study confirms that all subjects were healthy young males between the ages of 30 and 44.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

There were no imbalances in baseline characteristics between treatment groups.

Treatment Compliance and Concomitant Medications

There were no meaningful clinical differences in treatment compliance or use of concomitant

medications.

Efficacy Results – Primary Endpoint

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

Additional Analyses Conducted on the Individual Trial

Not applicable.

6.2. Study TADA-22-008

Overview and Objective

TADA-22-008: AN OPEN-LABEL, BALANCED, RANDOMIZED, SINGLE-DOSE, TWO-TREATMENT, TWO-SEQUENCE, TWO-PERIOD, TWO-WAY CROSSOVER, RELATIVE ORAL BIOAVAILABILITY STUDY OF TADALAFIL CHEWABLE TABLETS 20 MG (T), WITH CIALIS® (TADALAFIL) TABLETS 20 MG (R) IN HEALTHY ADULT MALE SUBJECTS UNDER FASTING CONDITIONS.

Trial Design

This was a single-dose, open-label, randomized, balanced, two-period, two-treatment, two-sequence, two-way crossover "*pilot*" BE study in 14 healthy adult male subjects. The primary study objective was to compare the relative bioavailability of Tadalafil Chewable Tablets 20 mg to Cialis Tablets 20 mg, each given under fasted conditions. Table 10 summarizes key elements of the study design.

Table 10: TADA-22-008 Study Design Overview

Study Type	Study ID	Objectives	Design	Regime Route	N
BE	TADA-21-008	*BE* Tadalafil Chewable Tablets (Fasted [T] vs. Cialis (Fasted [R])	SD, 2-way, X-over T (Fasted [A]) R (Fasted [B]) 0-72 hr PK 25 samples	Tadalafil Chewable Tablets, 20 mg, Fasted, Oral Chewed vs. Cialis Tablets, 20 mg, Oral Swallowed	Enrolled: 14 Dosed: Period 01: 14 Period 2: 13

Source: Table 11: Clinical Summary current submission

Primary Objectives:

- To assess the relative oral bioavailability of Tadalafil Chewable Tablets 20 mg (Treatment A) with Cialis (Tadalafil) 20 mg Tablets (Treatment B) in healthy adult male subjects under fasting conditions.

Secondary Objective:

- To monitor the safety and tolerability of single doses of investigational product when administered in healthy adult male subjects under fasting conditions.

Table 11: TADA-22-008 Study Description

Study Design	Single-dose, open-label, randomized, balanced, two-period, two-treatment, crossover study in healthy adult male subjects to assess oral bioavailability of Tadalafil Chewable Tablets 20 mg (A) and Tadalafil Tablets 20 mg (B, reference) under fasting conditions.
No. of Subjects	14
Housing	Subjects were housed in the clinic from at least 11.00 hours prior to dosing to at least 48.00 hours post-dose in each period.
Treatment Studied	A single dose of Tadalafil Chewable Tablets 20 mg under Fasting (Treatment A) conditions and a single dose of Cialis (Tadalafil) Tablets 20 mg (Treatment B) under Fasting conditions, when administered to subjects in a sitting posture with 240 mL of water.

Blood Sampling	Pre-dose (00.00 hour) and 00.17, 00.25, 00.33, 00.50, 00.75, 01.00, 01.33, 01.67, 02.00, 02.33, 02.67, 03.00, 03.50, 04.00, 04.50, 05.00, 06.00, 08.00, 12.00, 16.00, 24.00, 48.00, 72.00, 92.00 and 120.00 hours of post-dose in each period. The 96.00 and 120.00 hour samples were collected on an ambulatory basis.
Study Assessments	During the screening period, personal history, medical history, vital signs, physical examination, chest x-ray (within 6 months), 12 lead ECG, and hematology, biochemistry, urine analysis, and serology were assessed. During study, sitting blood pressure, pulse, and temperature were determined at check-in and at 1;00, 3:00, 7:00 and 12:00 hours of each post dose period and prior to checkout in each period.
Treatment Sequence	The order of investigational products assignment for each subject was determined according to the randomization schedule. Subjects were randomized to one of the two sequences: either AB or BA.
Washout Period	The interval between doses was 14 days.

Source: Overall Study Design and Plan Description, page 36, CSR TADA-21-008

Subjects were included in study based upon criteria comparable to those used in Study TADA-21-079 to which the reader is referred.

Subjects were excluded based upon criteria comparable to those used in Study TADA-21-079 to which the reader is referred.

Study Endpoints

The study endpoints were the typical PK parameters used to document bioequivalence.

- The 90% CI of the relative geometric mean of the Test (Treatment A) to Reference (Treatment B) formulation for Ln-transformed Cmax and AUC 0-72 should be within 80.00% to 125.00% to establish bioequivalence under fasting conditions.

Statistical Analysis Plan

See Study Endpoints

Protocol Amendments

The protocol was amended on April 19, 2022, with submission of a standardized product sensory attributes evaluation (in table form). The sensory attributes evaluated would include appearance, aroma, flavor, taste, sweetness, and mouth feel.

6.2.1. Study Results

Compliance with Good Clinical Practices

See the Clinical Pharmacology review.

Financial Disclosure

The Sponsor provided financial disclosure for this NDA submission. 2 investigators participated and neither had a financial disclosure.

Patient Disposition

14 subjects were dosed with the reference product (Treatment A) and 13 subjects were dosed with the test product (Treatment B). Overall, 13 subjects completed the study. One subject (Subject (b) (6)) withdrew consent towards the end of Period 1. No subject was removed from the study secondary to an adverse event.

Protocol Violations/Deviations

There were 28 missing blood samples during the study. Subject (b) (6) withdrew consent to continue in study and for that reason, 3 blood samples in Period 1 were not obtained for him at the 36, 48, and 72 post-dose timepoints in Period 1. Subject (b) (6) also had no blood samples in Period 2 (totaling 25 samples).

There were 6 subjects in whom the sampling times were delayed. The maximum delay time for a total of 9 samples was 6 minutes. This delay was secondary to difficulty with venous access. Sponsor states that none of the deviations impacted on subject safety or study outcome.

Demographic Characteristics

The study was conducted in Asian male healthy volunteers. All subjects were selected based on the absence of any clinically significant findings on the medical history, vital signs, well-being, physical examination, 12-lead ECG, chest X-ray (within past six months), screening clinical laboratory evaluations, urine drugs of abuse screen, and alcohol breath test. Subject satisfying all eligibility criteria were enrolled in the study. Review of the CRFs confirmed that all subjects were young healthy males. Table 12 provides a summary of key demographics for this study.

Table 12: Study TADA-22-008 Summary of Demographic Data

Demographic details of subjects who were enrolled the study (N= 14)				
Parameter	**Mean**	**SD**	**Min**	**Max**
Age (years)	32.1	4.74	23	42
Weight (kg)	67.6	8.65	56	81
Height (cm)	166.5	8.43	158	191
BMI (kg/m^2)	24.513	3.5413	19.61	29.75
Demographic details of subjects who were completed the study (N= 13)				
Parameter	**Mean**	**SD**	**Min**	**Max**
Age (years)	32.8	4.10	28	42
Weight (kg)	68.2	8.71	56	81
Height (cm)	165.9	8.48	158	191
BMI (kg/m^2)	24.874	3.4073	19.61	29.75

Source: Sponsor's Table 9 TADA-22-008 Study Report.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

There were no imbalances between treatment groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There were no clinically meaningful differences.

Efficacy Results – Primary Endpoint

This bioequivalence study was performed using a reformulated product as compared to the product used in TADA-21-079. The reformulated product is the to-be-marketed product.

Table 13 provides a summary of the mean PK parameter results collected in Study 008.

Table 13: Study TADA-22-008 Descriptive Statistics for Pharmacokinetic Parameters

Parameters (Units)	Tadalafil (Mean ± SD)	
	Treatment (A) (Test Fasted)	Treatment (B) (Reference Fasted)
Cmax (ng/mL)	402.758 ± 70.115	405.845 ± 80.523
AUC_{0-72} (ng*hr/mL)	13987.612 ± 4553.857	13576.279 ± 4346.237
Tmax (hr) [#]	2.35 (1.33 – 5.00)	2.67 (1.00 – 4.00)
t½ (hr)	46.606 ± 25.757	41.890 ± 17.165
Kel (1/hr)	0.0202 ± 0.0128	0.0193 ± 0.0077

([#]) Tmax is presented as median (minimum and maximum)

Source: Table 19 in Clinical Summary current NDA submission

Reviewer's Comment:

1. *In this pilot BE study (Study 079):*
   a. *The mean Cmax and AUC for the test and reference products are highly similar.*
   b. *The mean Tmax and mean half-lives are also comparable between the treatments. However, the mean half-life times for the test product (46.6 hours) and the reference product (41.9 hours) are greater than the mean half-life shown in approved Cialis labeling (17.5 hours). According to our colleagues in Clinical Pharmacology, the differences in half-life do not affect efficacy or safety because several non-clinically relevant factors, such as differences in bioanalysis methods, durations of blood sampling, numbers of Phase 1 studies pooled to obtain the mean half-life estimate, and methods of half-life calculation, could have played a role.*

Table 14 provides a summary of the BE comparison analysis for Study 008.

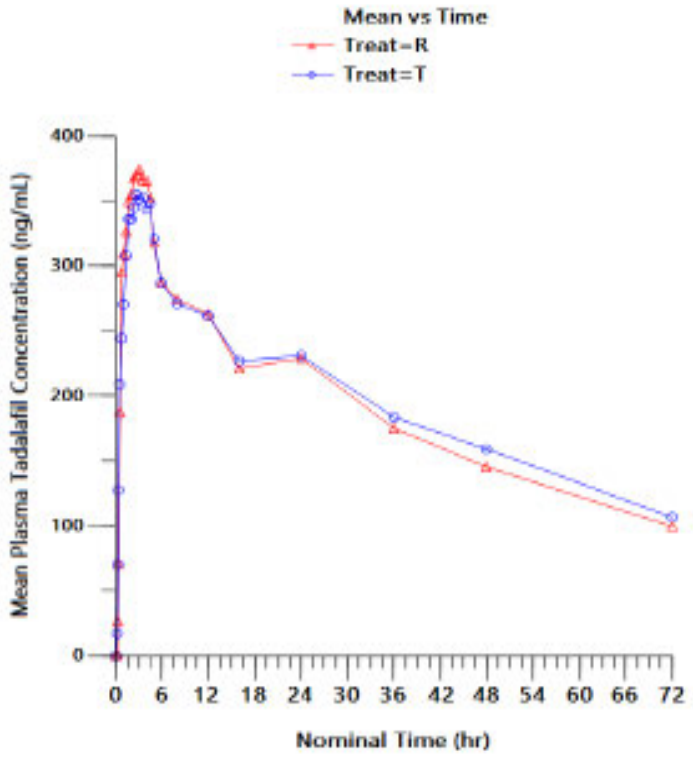
Table 14: Geometric Least Square Means Power (%), Test (T): Reference (R) Ratios, ISCV (%), 90% CI of Test (T) vs. Reference (R) for Tadalafil (fasted)

Parameters (Units)	Geometric Mean		Power (%)	ISCV (%)
	Test (A)	Reference (B)		
Cmax (ng/mL)	395.947	394.991	93.41	14.93
AUC_{0-72} (ng*hr/mL)	13174.513	12816.611	90.67	15.97
Parameters	**Ratio (%) A/B**	**90% CI A vs. B**	**Acceptance Criteria**	**BE Outcome**
Cmax	100.24	90.26% to 111.33%	80.00% - 125.00%	Bioequivalent
AUC0-72	102.79	91.89% to 114.99%	80.00% - 125.00%	

Treatment A = Tadalafil Chewable Tablets; (Test, Fasted); Treatment B = Cialis (Tadalafil) 20 mg Tablets (Reference, Fasted)

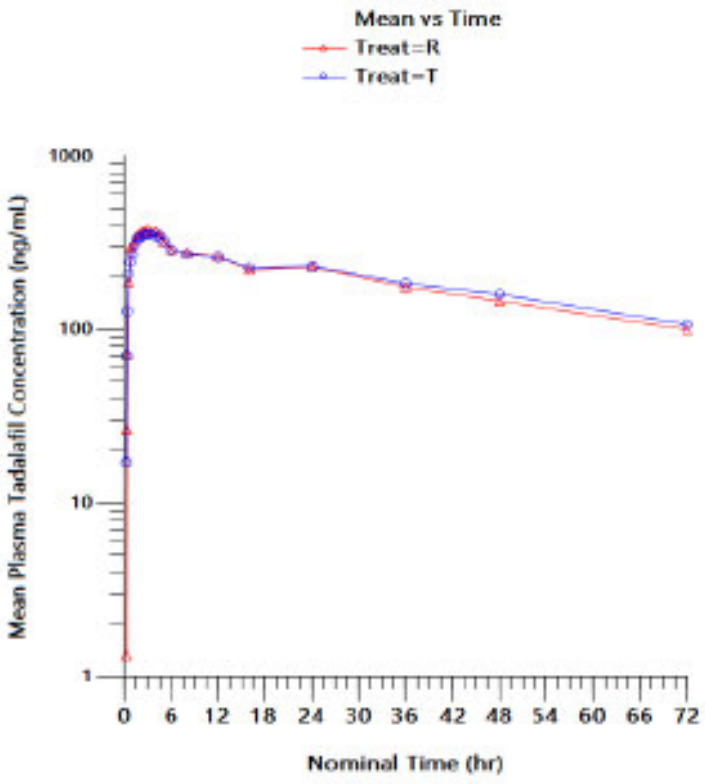
Source: Sponsor's Table 12 TADA-22-008 Study Report

Figure 2: Mean Tadalafil Plasma Concentrations vs Time (N=13) Study TADA-22-008



Source: Sponsor's Figure 3 Study TADA-22-008

Figure 3: Semi-log Plot of Mean Plasma Tadalafil Concentrations vs. Time (N=13)



Source: Figure 4 Study TADA-22-008

The Sponsor concluded:

> "The 90% CI of the geometric mean for Test to Reference formulations for Ln-transformed C_{max} and AUC_{0-72} were within 80.00% to 125.00%. Hence, the Test Product, Tadalafil Chewable Tablets 20 mg manufactured by [redacted] (b) (4), 70 Lake Drive, East Windsor, NJ 08520, USA and Reference Product Cialis (Tadalafil) Tablets 20 mg, marketed by Lilly USA, LLC Indianapolis, IN 46285, USA, are bioequivalent in healthy adult male subjects under fasting conditions."

Data Quality and Integrity

See Clinical Pharmacology review.

Efficacy Results – Secondary and other relevant endpoints

Not Applicable.

Dose/Dose Response

Not Applicable

Durability of Response

Not Applicable.

Persistence of Effect

The mean half-lives for Tadalafil Chewable Tablets (46.6 hours) and Cialis (41.9 hours) reported in this study are longer than the mean half-life reported for Cialis in approved labeling (17.5 hours).

> *Reviewer's Comment: According to the Clinical Pharmacology review team, the differences reported in half-life do not affect efficacy or safety because several non-clinically relevant factors, such as differences in bioanalysis methods, durations of blood sampling, numbers of Phase 1 studies pooled to obtain the mean half-life estimate, and methods of half-life calculation, could have played a role.*

Additional Analyses Conducted on the Individual Trial

No additional analyses were conducted.

6.3. Study TADA-22-051

Overview and Objective

A SINGLE-DOSE, OPEN-LABEL, RANDOMIZED, BALANCED, THREE-PERIOD, TWO-TREATMENT, THREE-SEQUENCE, CROSSOVER STUDY IN HEALTHY ADULT MALE SUBJECTS TO ASSESS THE RELATIVE ORAL BIOAVAILABILITY AND EFFECT OF FOOD ON TEST FORMULATION OF TADALAFIL CHEWABLE TABLETS 20 MG UNDER FED (TREATMENT A) AND FASTING (TREATMENT B) CONDITIONS WITH A REFERENCE FORMULATION OF CIALIS® (TADALAFIL) TABLETS 20 MG (TREATMENT C) UNDER FASTING CONDITIONS.

Trial Design

This was a single-dose, open label, randomized, balanced, three-period, two-treatment, three-sequence, three-way crossover, "*pivotal*" BE study in 42 healthy adult male subjects. Treatment A was 20mg Tadalafil Chewable Tablets in fed subjects, Treatment B was 20 mg Tadalafil Chewable Tablets in fasted subjects, and Treatment C was 20 mg Tadalafil Tablets (as reference) in fasted subjects.

The primary objectives of this study were to:

- Evaluate the relative oral bioavailability of Tadalafil Chewable Tablets 20 mg and Cialis (Tadalafil) 20 mg Tablets under fasting conditions.
- Evaluate the effect of food on the relative bioavailability of single dose Tadalafil Chewable Tablets 20 mg under fed and fasting conditions

The secondary objectives of this study were to:

- Assess the mucosal irritation potential of Tadalafil Chewable Tablets 20 mg (Treatment A and Treatment B) and Cialis (Tadalafil) 20 mg Tablets (Treatment C)
- Assess the safety and tolerability of single dose of investigational product when administered in healthy adult male subjects under fasting and fed conditions.

Table 15: TADA-22-051 Overall Study Design and Plan Description

Study Design	This was a single-dose, open label, randomized, balanced, three-period, two-treatment, three-sequence, three-way crossover study in 42 healthy adult male subjects.
No. of Subjects	42
Housing	Subjects were housed in the clinic from at least 11.00 hours prior to dosing to at least 48.00 hours post-dose in each period.
Treatment Studied	A single dose of Tadalafil Chewable Tablets 20 mg under Fed (Treatment A) and Fasting (Treatment B) conditions and a single dose of Cialis (Tadalafil) Tablets 20 mg (Treatment C) under Fasting condition when administered to subjects in a sitting posture with about 240 mL of water, in accordance with the randomization schedule.
Blood Sampling	Pre-dose (00.00 hour) and 00.17, 00.25, 00.33, 00.50, 00.75, 01.00, 01.33, 01.67, 02.00, 02.33, 02.67, 03.00, 03.50, 04.00, 04.50, 05.00, 06.00, 08.00, 12.00, 16.00, 24.00, 48.00, 72.00, 92.00 and 120.00 hours of post-dose in each period. The 96.00 and 120.00 hour samples were collected on an ambulatory basis.
Study Assessments	During the screening period, personal history, medical history, vital signs, physical examination, chest x-ray (within 6 months), 12 lead ECG, and hematology, biochemistry, urine analysis, and serology were assessed. Urine drugs of abuse and alcohol breath tests were performed at check-in prior to each period

	During the study, sitting blood pressure, pulse, and temperature were determined at check-in and at each blood sampling timepoint up to 48.00 hours post dose and prior to checkout in each period.
Treatment Sequence	The order of investigational products assignment for each subject was determined according to the randomization schedule. Subjects were randomized to one of the three sequences: either ABC, BCA, or CAB.
Washout Period	14 days

Source: Sponsor's Overall Study Design and Plan Description, page 45,C SR TADA-22-051.

Subjects were included in study based upon criteria comparable to those used in Study TADA-21-079, to which the reader is referred. Subjects were excluded based upon criteria comparable to those used in Study TADA-21-079, to which the reader is referred.

Study Endpoints

The study endpoints were the typical pharmacokinetic parameters used to document bioequivalence:

- The 90% CI of the relative geometric mean of the Test (Treatment B - fasting dosing without water) to Reference (Treatment C - fasting dosing with water) formulation for Ln-transformed Cmax and AUC 0-72 should be within 80.00% to 125.00% to establish bioequivalence under fasting conditions.

Statistical Analysis Plan

See discussion of Study Endpoints

Protocol Amendments

The protocol was issued March 25, 2023, as Version 1.

Amendment No. 1 was issued April 4, 2023, as protocol Version 2. It modified the evaluation of product sensory attributes. The evaluation was modified to include subject indicating (1) if he had any difficulty chewing the tablet and (2) whether he accidentally swallowed the tablet intact.

The last paragraph of Evaluation of Sensory Attributes was modified to read "In Part 2, the subjects is queried about taste perceptions ("Sour", "Salty", "Sweet", "Bitter" and "Savoury") on an 11-point Numerical Rating Scale (NRS) anchored on the left and right by 0 and 10, respectively, where 0 = "Not at All" and 1 0 = "Extremely". The subject is then prompted to

provide a response to "Smell" on an 11-point NRS anchored on the left and right by 0 and 1 0, respectively, where 0 = "No Smell" and 1 0 = "Extreme Smell".

Amendment No.2 was issued April 10, 2023, as protocol Version 3. The 6 protocol modifications are shown in the bullet points below:

1) **2.0 PROTOCOL SYNOPSIS, Objectives, Secondary Objectives now reads:**
   - To assess the mucosal irritation potential of Tadalafil Chewable Tablets 20 mg Test formulation without water (Treatment A) and Tadalafil Chewable Tablets 20 mg Test formulation with water (Treatment B).
   - To monitor the safety and tolerability of a single dose of investigational product when administered in healthy human adult male subjects under fasting conditions.

2) **2.0 PROTOCOL SYNOPSIS, Bioequivalence Criteria now reads:**
   - The 90% confidence interval of the relative mean (geometric mean) of the Test formulation without water {Treatment A) and the Test formulation with water {Treatment B) for Ln-transformed Cmax and AUC for tadalafil should be within 80.00% to 125.00% to establish bioequivalence.

3) **7.0 OBJECTIVES, Secondary Objective now reads:**
   - To assess the mucosal irritation potential of Tadalafil Chewable Tablets 20 mg Test formulation without water (Treatment A) and Tadalafil Chewable Tab lets 20 mg Test formulation with water {Treatment B).
   - To monitor the safety and tolerability of a single dose of investigational product when administered in healthy human adult male subjects under fasting conditions.

4) **16.0 PHARMACOKINETIC AND STATISTICAL ANALYSIS, 16.1 Pharmacokinetic Analysis (**This is a title change. No text change)

5) **Mucosa Irritation Assessment (new text)**
   - Mucosal Irritation Assessments will be completed by (i) the subject under the supervision of trained study personnel; and (ii) the Principal Investigator, Clinical Investigator or Medical Officer ("Study Physician") within 40 minutes prior to dosing (00.00 hour) and at 00.50, 01 .00, and 12.00 hours of post dose (±I O-minute) in each period {Treatment A and Treatment B). The subject scale is a 10-point self-report outcome (0 = None, 1 to 4 = Mild, 5 to 7 = Moderate, 8 to 9 = Severe, > 9 = Very Severe) for (i) Itching; (ii) Burning sensations; (iii) Difficulty swallowing; and (iv) Taste changes. Mucosal Irritation Assessment by the Study Physician will utilize a 4-point (0-3) Physician Assessment Score, where: 0 = None (Normal), 1 = Erythema plus slight edema (Mild), 2 = Moderate erythema and/or edema (beginning of tissue breakdown or sloughing) (Moderate), and 3 = Severe inflammation/irritation (definite blistering, ulceration, or epithelial sloughing. The following statistical analysis will be performed on mucosal irritation data for subject's self-report and Study Physician's oro-mucosal assessment. i) Change in mucosal irritation scores from pre-dose (00.00 hour) to each post-dose time point (00.50, 01.00

and 12.00 hours) for the Test product without water (Treatment A) and the Test product with water (Treatment B) at the 5% level of significance. Subjects for whom mucosal irritation data are missing for Treatment A or Treatment B will not be included in the analysis. ii) Change in mucosal irritation scores will be compared over post-dose time points (00.50, 01.00 and 12.00 hours) for the Test product without water (Treatment A) and the Test product with water (Treatment B) at the 5% level of significance. All the available assessment data of from subjects will be included in the analysis. Data for each mucosal irritation variable ("Itching", "Burning Sensation", "Difficulty Swallowing" and "Taste Changes") will be summarized as the Mean ± SD by time point and treatment (Treatment A and Treatment B).

If any data contains only scores of '0' then no comparison will be made.

A frequency Table with count and percentage (%) will be provided for each variable by time point and formulations (Test and Reference).

6) 16.2 Sensory Attributes (new text)

- Evaluation of Sensory Attributes will be performed by the subject under the supervision of trained study personnel immediately (i.e., within 2-minutes) after drug administration of Chewable tablets only. In Part 1, sensory attribute data ("Appearance", "Aroma", "Taste", "Mouth-feel and "Flavour Intensity") will be collected immediately after administration of the chewable Test product (Treatment A and Treatment B) using a 9-point hedonic Likert scale (1 = Dislike Extremely; 2 = Dislike Very Much; 3 = Dislike Moderately; 4 = Dislike Slightly; 5 = Neither Like Nor Dislike; 6 = Like Slightly; 7 = Like Moderately; 8 = Like Very Much; 9 = Like Extremely and summarized as mean ± SD. Flavour description will be summarized as count (%) of flavours for test formulation (Treatment A and Treatment B). Difficulty thoroughly chewing the tablet and accidental swallowing of intact tablet will be summarized as count (%) for Test formulation (Treatment A and Treatment B). In Part 2, additional sensory attribute data about taste perceptions ("Sour", "Salty", "Sweet", "Bitter" and "Savoury") on an 11-point Numerical Rating Scale (NRS) anchored on the left and right by 0 and 10, respectively, where 0 = "Not At All" and 10 = "Extremely". The subject will then be prompted to provide a response to "Smell" on an 11-point NRS anchored on the left and right by 0 and 10, respectively, where 0 = "No Smell" and 10 = "Extreme Smell."

Compliance with Good Clinical Practices

Quality Assurance personnel assessed compliance with study requirements as per Good Clinical Practices, internal SOPs, study protocol and applicable regulatory requirements.

Financial Disclosure:

The Sponsor provided financial disclosure for this NDA submission. A total of 3 investigators participated and none had financial disclosures to report.

Patient Disposition

In this study, 42 (+ 02 standby subjects, standby (b) (6) and standby (b) (6) healthy adult male subjects were enrolled. 42 subjects were dosed in Period 01 (after completion of 42 subjects dosing, standby subjects were checked-out from the facility), 39 subjects were dosed in Period 02, and 39 subjects were dosed in Period 03. In total, 39 subjects completed at least 2 study periods and 37 subjects completed all 03 study periods in accordance with protocol.

39 subjects received Treatment A which was 20 mg Tadalafil Chewable Tablet in Fed conditions (Subjects (b) (6) did not receive Treatment A). 40 subjects received Treatment B which was 20 mg Tadalafil Chewable Tablets in fasted condition (Subjects (b) (6) did not receive Treatment B). 41 subjects received Treatment C which was 20 mg Cialis (tadalafil) tablet under fasted condition (Subject (b) (6) did not receive Treatment C). 37 subjects completed all 3 study periods.

Subjects not completing all 3 treatment arms are summarized below:

- Subject (b) (6) was withdrawn due to an adverse event (fever) during Period 3.
- Subject (b) (6) was withdrawn during period 2 after an alcohol breath test was positive
- Subjects (b) (6) failed to report for Period 2 but did report for Periods 1 and 2 and were included for pharmacokinetic and statistical analysis.
- Subject (b) (6) did not report for Period 2 and Period 3 check-in. He was not dosed with reference product.

In the bioequivalence analysis group, the following subjects were excluded from the statistical analysis:

- Subject (b) (6), who was withdrawn secondary to fever.
- Subject (b) (6), who was withdrawn due to protocol non-compliance with a positive alcohol breath test.
- Subject (b) (6), who did not report for Periods 2 and 3 check-in.

In the food effect analysis group, the following subjects were excluded from the statistical analysis:

- Subjects (b) (6), who did not report for Period 2 check-in.
- Subject (b) (6) who was withdrawn due to adverse event (fever) prior to Period 3 dosing.
- Subject (b) (6) who was withdrawn due to protocol non-compliance with a positive alcohol breath test.
- Subject (b) (6) who did not report for the Periods 2 and 3 check-in.

Protocol Violations/Deviations

Blood sampling

There were 173 missed blood samples during the study. This included: (i) 168 samples from 5 subjects who were withdrawn from the study (2 subjects) or who failed to report to the study

facility (3 subjects); (ii) 3 post-checkout ambulatory samples (1 sample in 3 subjects); and (iii) 2 post-checkout ambulatory samples in 1 subject with a positive alcohol breath test

There were 17 subjects who experienced a delay in scheduled blood sampling times. All delays were below 6 minutes and are unlikely to impact upon patient safety or efficacy outcome, in this reviewer's opinion. All deviations were secondary to difficulty with venous access.

Mucosal Irritation Assessment
In Period 2, for Subject (b) (6) the 12-hour mucosal assessment was not documented due to medical officer oversight error. This is not believed to have impacted on subject safety.

In Period 1, for Subjects (b) (6), the pre-dose (00.00 hours), Mucosal Irritation Assessment was performed with a time deviation. This is not believed to have impacted on subject safety.

Post-Study Safety Assessment
For subject (b) (6) the post-study sample was not collected, as the subject did not report to the study facility for Period 03 for his 120.00-hour ambulatory sample. The study also required a clinical examination, including vital signs (sitting blood pressure, pulse rate and body temperature) at the end of study. A post-study blood sample was collected the next day and it reported laboratory values within the normal range. Similarly, a clinical examination on the next day was found to be normal. The study physician believes this deviation did not impact on subject safety

Pharmacokinetic, Statistical analysis and CDISC deliverables facility change.
Pharmacokinetic analysis was performed at a different (b) (4) facility than specified in protocol. All generated data was reviewed by a biostatistician. Sponsor concluded there was no impact on the study outcome.

Table of Demographic Characteristics

Table 16: Demographic Details of Subjects Enrolled in Study TADA-22-051 (N=42 = 02 Standby)

Demographic details of subjects who were enrolled the study (N= 42+02 Standby)				
Parameter	**Mean**	**SD**	**Min**	**Max**
Age (years)	35.5	5.46	22	41
Weight (kg)	71.2	10.35	53	96
Height (cm)	167.3	6.52	156	183
BMI (kg/m^2)	25.382	2.9270	19.36	29.71
Demographic details of subjects who were completed the study (N= 39)*				
Parameter	**Mean**	**SD**	**Min**	**Max**
Age (years)	35.7	5.56	22	41
Weight (kg)	72.3	9.89	53	96
Height (cm)	167.5	6.52	156	183
BMI (kg/m^2)	25.719	2.8119	19.47	29.71

Note: *39 subjects completed 02 periods of the study and 37 subjects completed 03 periods of the study.

Source: Sponsor's Snapshot of Table 14 page 72 CSR.

The study was conducted in young, healthy Asian male volunteers. All subjects were selected based on the absence of any clinically significant findings on the medical history, vital signs, well-being, physical examination, 12-lead ECG, chest X-ray (within past six months), screening clinical laboratory evaluations, urine drugs of abuse screen and alcohol breath test. Subject satisfying all eligibility criteria were enrolled in the study. Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

There were no imbalances between treatment groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There were no meaningful clinical differences.

6.3.1. Efficacy Results

Efficacy Results – Primary Endpoint

This pivotal bioequivalence study was performed using a reformulated product as compared to the product used in the pilot bioequivalence study TADA-21-079. The reformulated product is the to-be-marketed product.

Table 17 provides a summary of the key PK results of Study 051.

Table 17: Selected Descriptive Statistics for Tadalafil as Chewable Tablets and as Cialis Tablet TADA-21-051

Median/ Geometric Mean	Cmax (ng/mL)	AUC 0-4 (hr*ng/mL)	Tmax (hr)	T1/2 (hr)
Tadalafil Chewable Tablets FED (A)	299.347/ 306.883	116058.244/ 4731.379	5.00/ 6.96	32.059/ 31.985
Tadalafil Chewable Tablets FASTED (B)	331.366/ 356.006	14405.554/ 13321.887	2.67/ 2.58	32.131/ 32.201
Cialis Fasted (C)	374.473/ 366.852	14171.899/ 13666.118	2.67/ 2.46	33.110/ 33.469

Source: Tables 15, 16, 17, excerpted for selected parameters.

Reviewer's Comments

1. *In this study, the tadalafil half-lives for all 3 treatment arms, including Cialis Tablets, are prolonged as compared to the half -life of 17.5 hours shown in approved Cialis labeling. The Clinical Pharmacology review team stated that differences in half-lives observed between this chewable tablet and the current approved product will have no effect on efficacy or safety. The difference in half-life reflects differences in other parameters including methodology of calculating the half-life and the study populations in the trials used to calculate the half-life.*
2. *There was a moderate food effect on Tmax: that is, a longer time to Cmax for Tadalafil Chewable Tablets fed (5 hours) compared to Tadalafil Chewable Tablets fasted (2.67 hours) and Cialis fasted (2.67 hours). This raised a concern about the potential for delayed efficacy. In our 74-Day letter to Sponsor, we asked the Sponsor to comment. In their response dated December 25, 2023, the Sponsor submitted published literature to support the product's benefit in fed patients. They stated that concentrations achieved in fed patients are greater than demonstrably effective concentrations in the studies provided in the literature references. The Sponsor concluded that the long half-life and relatively flat tadalafil PK curve provide additional assurance that the delay in Tmax in fed subjects would be of no clinical significance. The Clinical Pharmacology review team concurred that concentrations of tadalafil in fed subjects with Tadalafil Chewable 20 mg doses exceeded those noted at 15 minutes when first erectile events were observed in the published study. Based on this evidence and analysis, and in consideration of the product labeling and relatively flat tadalafil PK curve, we agree that clinical benefit (efficacy) in fed subjects is not adversely affected from a clinical perspective.*

Table 18: Fasted Geometric Least Square Means, Power (%), 90% CI Test (Treatment B)/ Reference (Treatment C) Ratios and ISCV (%)

Parameters (Units)	Geometric Mean (N=39)		Power (%)	ISCV (%)
	Test (B)	Reference (C)		
C_{max} (ng/mL)	356.006	366.852	100.0	14.22
AUC_{0-t} (hr*ng/mL)	13321.887	13666.118	100.0	14.15
Parameters	**Ratio (%)** B/C	**90% Confidence Intervals for B vs. C**	**Acceptance Criteria**	**Outcome of BE result**
C_{max}	97.04	91.93% to 102.44%	80.00% - 125.00%	Bioequivalent
AUC_{0-t}	97.48	92.37% to 102.87%	80.00% - 125.00%	

ISCV = intrasubject variability
Source: Sponsor's Snapshot Table 18 in TADA-22-051 CSR

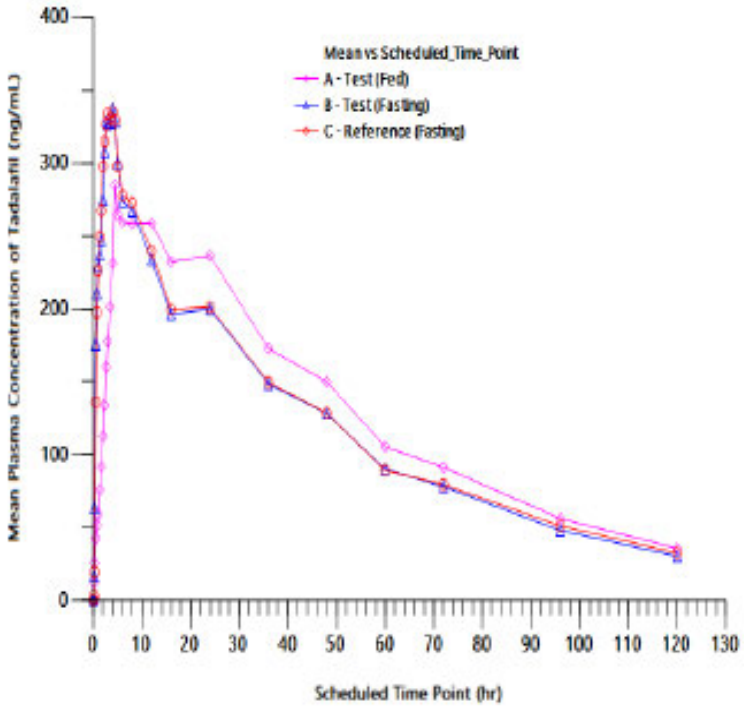
Table 19: Fed (Treatment A)/ Fasted (Treatment B) Geometric Least Square Mean, Power (%), Ratios and 90% CI, and ISCV (%)

Parameters (Units)	Geometric Mean (N=37)		Power (%)	ISCV (%)
	Test (A)	Test (B)		
C_{max} (ng/mL)	306.750	351.817	98.42	22.06
AUC_{0-t} (hr*ng/mL)	14751.664	13205.974	100.0	13.73
Parameters	**Ratio (%)** A/B	**90% Confidence Intervals for A vs. B**	**Acceptance Criteria**	**Outcome of BE result**
C_{max}	87.19	80.01% to 95.02%	80.00% - 125.00%	Bioequivalent
AUC_{0-t}	111.70	105.84% to 117.89%	80.00% - 125.00%	

Source: Sponsor's Snapshot Table 19 in TADA-22-051 CSR.

Reviewer's Comment: Tadalafil Chewable Tablets Treatment A (Fed) and Tadalafil Chewable Tablets Treatment B (Fasting) were bioequivalent for the key Cmax and AUC PK parameters.

Figure 4: Linear Plot of Mean Plasma Tadalafil Concentrations vs Time (N=39) TADA-22-051



*N=37 for Test, Fed (Treatment A); N=39 for Test, Fasted (Treatment B); N=39 for Reference, Fasted (Treatment C).

Source: Sponsor's Figure 3 TADA-22-051 CSR

Data Quality and Integrity

See the Clinical Pharmacology review.

Efficacy Results – Secondary and other relevant endpoints

See the Efficacy Results section.

Dose/Dose Response

Not Applicable.

Durability of Response

Not Applicable.

Persistence of Effect

The mean half-lives for Tadalafil Chewable Tablets (approximately 32 hours) and Cialis (approximately 33 hours) reported in this study exceed the mean half-life reported for Cialis in approved labeling (17.5 hours).

> *Reviewer's Comment: After review by the Clinical Pharmacology review team, differences between this chewable tablet and the approved product in half-life do not affect efficacy or safety because several non-clinically relevant factors, such as differences in bioanalysis methods, durations of blood sampling, numbers of Phase 1 studies pooled to obtain the mean half-life estimate, and methods of half-life calculation, could have played a role.*

Additional Analyses Conducted on the Individual Trial

Not Applicable.

6.4. Study TADA-23-023

Overview and Objective

A SINGLE-DOSE, OPEN-LABEL, RANDOMIZED, BALANCED, TWO-PERIOD, ONE-TREATMENT, TWO-SEQUENCE, CROSSOVER STUDY TO ASSESS THE RELATIVE ORAL BIOAVAILABILITY OF TEST FORMULATION TADALAFIL CHEWABLE TABLETS 20 MG ADMINISTERED WITHOUT WATER (TREATMENT A) COMPARED WITH TADALAFIL CHEWABLE TABLETS 20 MG ADMINISTERED WITH WATER (TREATMENT B) IN HEALTHY ADULT MALE SUBJECTS UNDER FASTING CONDITIONS.

Trial Design

This was a single-dose, open-label, randomized, balanced, two-period, one treatment, two-sequence, crossover study in healthy adult male subjects to assess the relative oral bioavailability of 20 mg of investigational product (Tadalafil Chewable Tablets) when administered *with and without water* under fasting conditions.

Primary Objectives:

- To assess the relative oral bioavailability of Test formulation Tadalafil Chewable Tablets 20 mg administered without water (Treatment A) when compared with Tadalafil Chewable Tablets 20 mg administered with water (Treatment B) in healthy adult male subjects under fasting conditions.

Secondary Objectives:

- To assess the relative oral bioavailability of Test formulation Tadalafil Chewable Tablets 20 mg administered without water (Treatment A) when compared with Tadalafil

Chewable Tablets 20 mg administered with water (Treatment B) in healthy adult male subjects under fasting conditions.

- To monitor the safety and tolerability of single doses of investigational product when administered in healthy adult male subjects under fasting and fed conditions.

Table 20: Overall Study Assessments Study TADA-23-023

Study Design	Single-dose, open-label, randomized, balanced, two-period, one-treatment, two-sequence, crossover study in healthy adult male subjects to assess the relative oral bioavailability of 20 mg of investigational product when administered without water (Treatment A) and with water (Treatment B) under fasting conditions.
No. of Subjects	18
Housing	Subjects were housed in the clinic from at least 11.00 hours prior to dosing to at least 48.00 hours post-dose in each period.
Treatment Studied	A single dose of Tadalafil Chewable Tablets 20 mg under Fasting conditions administered to subjects in a sitting posture with 240 mL of water and without water.
Blood Sampling	Pre-dose (00.00 hour) and 00.17, 00.25, 00.33, 00.50, 00.75, 01.00, 01.33, 01.67, 02.00, 02.33, 02.67, 03.00, 03.50, 04.00, 04.50, 05.00, 06.00, 08.00, 12.00, 16.00, 24.00, 48.00, 72.00, 92.00 and 120.00 hours of post-dose in each period. The 96.00 and 120.00 hour samples were collected on an ambulatory basis.
Study Assessments	During the screening period, personal history, medical history, vital signs, physical examination, chest x-ray (within 6 months), 12 lead ECG, and hematology, biochemistry, urine analysis, and serology were assessed. Urine for drugs of abuse and alcohol breath tests were performed at check-in for each study period. During study, sitting blood pressure, pulse, and temperature were determined at check-in and at each blood sampling timepoint up to 48.00 hours post dose and prior to checkout in each period.

Treatment Sequence	The order of investigational products assignment for each subject was determined according to the randomization schedule. Subjects were randomized to one of the two sequences: either BA or AB
Washout Period	The interval between doses was 14 days.

Source: Study Design and Plan Descriptions, CSR TADA-23-023

Subjects were included in study based upon criteria comparable to those used in Study TADA-21-079, to which the reader is referred.

Subjects were excluded based upon criteria comparable to those used in Study TADA-21-079, to which the reader is referred.

Study Endpoints

The study endpoints were the key PK parameters used to document bioequivalence.

- The 90% CI of the relative geometric mean of the Test Product administered without water Treatment A) to Test Product administered with water (Treatment) for Ln-transformed Cmax and AUC 0-72 should be within 80.00% to 125.00% to establish bioequivalence under fasting conditions.

Statistical Analysis Plan

See discussion of Study Endpoints

Protocol Amendments

The protocol was amended on October 22, 2021, with submission of the standardized meal plan.

6.4.1. Study Results

Compliance with Good Clinical Practices

See the Clinical Pharmacology review.

Financial Disclosure

The Sponsor provided financial disclosure for this NDA submission. 3 investigators participated and none had financial disclosure.

Patient Disposition

Twenty-four healthy adult male subjects were enrolled, 24 subjects were dosed in Period 01, 22 subjects were dosed in Period 02 (subject (b) (6) vomited in Period 01 soon after dosing; and subjects (b) (6) withdrew their consent to participate in the study in Period 01 and Period 02, without providing a reason). Therefore, 21 subjects completed both study periods.

Protocol Violations/Deviations

There were 9 subjects who had minimal delays in blood sampling secondary to difficulty with venous access. There were two subjects who arrived late for blood sampling: (b) (6) arrived 169 minutes late for the 120.00 hours sampling (Treatment A) and (b) (6) arrived 146 minutes late for the 96 hour sampling time (Treatment B).

There were 85 missed samples during the study. This included (i) 43 samples from 02 subjects who withdrew consent in either Period 01 or Period 02; (ii) 40 samples (12 samples in Period 01 and 28 samples in Period 02) from 01 subject who vomited before 02 times the median t_{max} of investigational product; and (iii) 02 samples from 01 subject who did not report for ambulatory sampling visits.

> *Reviewer's Comment: Regarding the impact of the late or missed samples, see the Clinical Pharmacology review.*

Demographic Characteristics

Table 21: Summary of Demographic Data TADA-23-023

Demographic details of subjects who were enrolled in the study (N= 24)				
Parameter	**Mean**	**SD**	**Min**	**Max**
Age (years)	33.0	7.25	19	43
Weight (kg)	68.7	11.84	54	91
Height (cm)	169.2	5.96	159	180
BMI (kg/m^2)	23.987	3.7739	19.04	29.75
Demographic details of subjects who were completed the study (N= 21)				
Parameter	**Mean**	**SD**	**Min**	**Max**
Age (years)	32.7	7.53	19	43
Weight (kg)	67.6	11.62	54	91
Height (cm)	169.3	5.80	159	180
BMI (kg/m^2)	23.589	3.7426	19.04	29.75

Source: Sponsor's Table 11 CSR TADA-23-023

The study was conducted in young, healthy Asian male subjects. All subjects were selected based on the absence of any clinically significant findings on the medical history, vital signs, wellbeing, physical examination, 12-lead ECG, chest X-ray (within past six months), screening clinical laboratory evaluations, urine drugs of abuse screen and alcohol breath test. Subjects satisfying all eligibility criteria were enrolled in the study. All laboratory values had to be normal, non-reactive, negative, or not clinically significant as determined by the investigator.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

There were no imbalances between treatment groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

There were no meaningful clinical differences.

Efficacy Results – Primary Endpoint

Table 22 provides summary statistics for select PK parameters (Cmax, AUC, Tmax and $T_{1/2}$) from Study 023.

Table 22: Selected Descriptive Statistics Treatments A and B Under Fasting Conditions TADA - 23-023

Median/ Geometric Mean	Cmax (ng/mL)	AUC $_{0-4}$ (hr*ng/mL)	Tmax (hr)	$T_{1/2}$ (hr) *
Tadalafil Chewable Tablets Test A (Without water)	303.905/ 322.435	10544.499/ 10409.479	2.70/ 2.81	26.998/ 26.672
Tadalafil Chewable Tablets Test B (With water)	349.926/ 339.435	10850.935/ 10612.816	2.67/ 2.45	26.113/ 26.297

Sources: Tables 12 and 13 CSR TADA-23-023

Reviewer's Comments: In this study, tadalafil half-lives for all both treatment arms, including Cialis Tablets are prolonged (approximately 26-27 hours) as compared to the half -life of 17.5 hours shown in approved Cialis labeling. After review by the Clinical Pharmacology review team, the differences in half-life between the proposed and approved products will not affect efficacy or safety of the new chewable tablet.

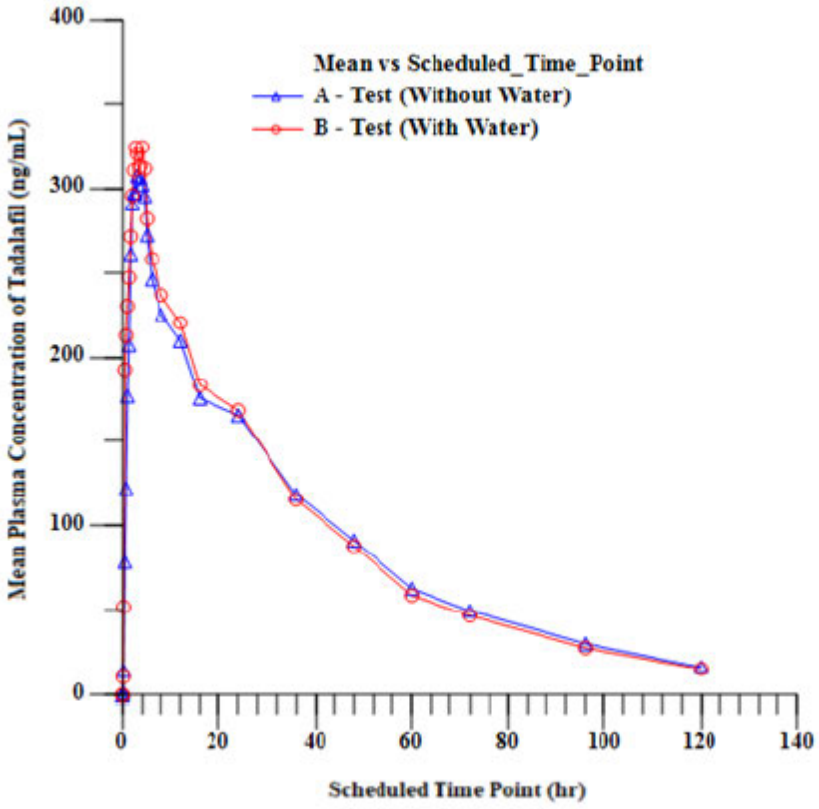
Table 23: Geometric Least Square Mean, Power (%), Ratios (A vs. B), ISCV (%) and 90% CI (A vs. B)

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%
Parameters	**Ratio (%)**	**90% Confidence Intervals for A vs. B**	**Acceptance Criteria**	**Outcome of BE result**
	A/B			
C_{max}	95.13%	88.9% to 101.81%	80.00% - 125.00%	Bioequivalent
AUC_{0-t}	98.41%	91.98% to 105.28%	80.00% - 125.00%	

Source: Sponsor's Snapshot Table 14 CSR TADA-23-023

Reviewer's Comment: Tadalafil Chewable Tablets Treatment A (Without water) and Tadalafil Treatment Chewable Tablets B (With water) were bioequivalent for the key Cmax and AUC PK parameters.

Figure 5: Linear Plot of Mean Tadalafil Concentrations (ng/mL) vs Time (N-21) Tada-23-023



Source: Sponsor's Snapshot Figure 3 CSR TADA-23-023

Data Quality and Integrity

See the Clinical Pharmacology review

Efficacy Results – Secondary and other relevant endpoints

See the Clinical Pharmacology review

Dose/Dose Response

See the Clinical Pharmacology review.

Durability of Response

Not Applicable.

Persistence of Effect

The mean half-lives for Tadalafil Chewable Tablets (approximately 26-27 hours) reported in this study exceed the mean half-life reported for Cialis in approved labeling (17.5 hours).

> *Reviewer's Comment: According to the Clinical Pharmacology review team, the differences in half-life do not affect efficacy or safety because several factors that are not clinically relevant, such as differences in bioanalysis, durations of blood sampling, numbers of Phase 1 studies pooled to obtain the mean half-life estimate, and methods of half-life calculation, could have played a role.*

Additional Analyses Conducted on the Individual Trial

Not Applicable

> *Reviewer's Comment: In this study (Study 023), Tadalafil Chewable Tablets demonstrated bioequivalence when taken with or without water.*

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

The Sponsor has provided data that demonstrates bioequivalence between Tadalafil Chewable Tablets 20 mg and Cialis 20 mg.

7.1.1. Primary Endpoints

In Study 051, bioequivalence (for Cmax and AUC) has been demonstrated between Tadalafil Chewable Tablets 20 mg and Cialis 20 mg (Study 051). Also in Study 051, bioequivalence (Cmax and AUC) was demonstrated between Tadalafil Chewable Tablets 20 mg in fed and fasting state. Although Tmax was delayed in the fed state compared to fasting, the delay was considered to have no clinical impact on efficacy. In Study 023, bioequivalence was demonstrated between Tadalafil Chewable Tablets with or without water. The reader is referred our reviews of the individual trial results in Section 6 of this review for detailed information. The results are summarized in the table below.

Table 24: Selected Comparative Pharmacokinetic Parameters

Study	T or R*	Fed or Fast	N	AUC_{0-t} (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	T_{max} (hr)/$T_{1/2}$ (hr) *$T_{1/2}$ (hr) italicized*
TADA-22-008	T	Fast	14	13987.612 ± 4553.857#	ND	402.758 ± 70.115	2.35 (1.33 – 5.00)/ *46.006*
TADA-22-008	R	Fast	14	13576.279 ± 4346.237#	ND	405.845 ± 80.523	2.67 (1.00 – 4.00)/ *41.890*
TADA-22-051	T	Fed	42	15328.463 ± 4122.5815*	17497.082 ± 5529.0061	313.011 ± 64.4890	5.00 (4.00 –24.07)/ *34.049*
TADA-22-051	T	Fast	42	14077.480 ± 4485.0696*	16153.046 ± 5953.4773	368.714 ± 101.5119	2.67 (0.50 – 4.50)/ *34.739*
TADA-22-051	R	Fast	42	14272.512 ± 4134.0367*	16537.536 ± 5943.9809	377.540 ± 87.8398	2.67 (0.75 – 4.50)/ *33.469*
TADA-23-023 Without water	T	Fast	24	10916.854 ± 3367.8937*	12127.330 ± 4360.1408	330.222 ± 75.7878	2.70 (1.00 – 4.50)/ *29.37*
TADA-23-023 With water	T	Fast	24	11030.931 ± 2903.8310*	12236.253 ± 4029.6379	347.260 ± 71.9933	2.67 (0.50 – 4.53)/ *29.32*

*Test (T) or Reference(R)

Sources: Sponsor's Table 35 Clinical Summary, Tables 12 and 13 CSR TADA-23-023, Tables 15, 16, 17, CSR TADA-21-051, and Table 19 CSR TADA-22-008. Note: Study TADA-21-079 did not use the to-be-marketed formulation and is not included in the table.

Regarding a difference between Tmax for Tadalafil Chewable Tablets fasted vs fed (5 hours as opposed to 2.67 hours), based on Sponsor-cited literature, the Clinical and Clinical Pharmacology review teams determined that tadalafil concentrations achieved in fed patients are greater than demonstrably effective concentrations in the studies provided in the literature references. Based on this evidence and analysis, and in consideration of the product labeling and relatively flat tadalafil PK curve, we agree that clinical benefit (efficacy) is not adversely affected by these reported differences.

Regarding a difference between half-lives for Tadalafil Chewable Tablets and Cialis in the Sponsor's four BE studies compared to Tmax for Cialis in FDA-approved labeling, the mean half-lives were comparable between the treatments. However, the mean half-life times for the Tadalafil Chewable Tablets and Cialis (26- 46 hours) were greater than the mean half-life shown

in approved Cialis labeling (17.5 hours). According to our colleagues in Clinical Pharmacology, the differences in half-life do not affect efficacy or safety because several non-clinically relevant factors, such as differences in bioanalysis methods, durations of blood sampling, numbers of Phase 1 studies pooled to obtain the mean half-life estimate, and methods of half-life calculation, could have played a role. In addition, Tadalafil Chewable Tablets and Cialis were clearly bioequivalent for Cmax and AUC. Taken together, the submitted NDA information supports a conclusion that the observed differences in half-lives in the Sponsor's BE studies and in approved Cialis labeling do not affect product performance.

7.1.2. Secondary and Other Endpoints

See Section 7.1.1 immediately above.

7.1.3. Subpopulations

Not Applicable.

7.1.4. Dose and Dose-Response

The difference in mean Tmax between fed (5 hours) and fasted (2.67 hours) subjects dosed with Tadalafil Chewable Tablets does not raise an efficacy concern as tadalafil concentrations achieved in fed patients are greater than demonstrably effective concentrations in the studies provided in the literature references. The reported differences are likely related to the relatively flat PK curves for tadalafil.

Onset, Duration, and Durability of Efficacy Effects

Regarding differences in Tmax with food, see Section 7.1.4 and previous Reviewer's Comments.

Regarding differences in half-lives between Tadalafil Chewable Tablets and Cialis in the Sponsor's four BE studies (approximately 26-46 hours) and approved Cialis labeling (17.5 hours), these do not affect efficacy or safety because several non-clinically relevant factors, such as differences in bioanalysis methods, durations of blood sampling, numbers of Phase 1 studies pooled to obtain the mean half-life estimate, and methods of half-life calculation, could have played a role. In addition, Tadalafil Chewable Tablets and Cialis were clearly bioequivalent for the parameters Cmax and AUC. Taken together, the submitted information supports a conclusion that the observed differences in half-lives in the Sponsor's BE studies and in approved Cialis labeling do not affect product performance.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are no additional efficacy issues that require further consideration in the postmarketing

setting.

7.2.2. Other Relevant Benefits

For some subjects, a chewable tablet that may be taken without water may make it easier to use the tadalafil product as opposed to swallowing an intact tadalafil tablet.

7.3. Integrated Assessment of Effectiveness

This is a 505(b)(2) submission. The Sponsor has established an acceptable clinical bridge through comparative bioavailability studies TADA-22-008, TADA-22- 051 and TADA-23-023 to the reference product Cialis(tadalafil) 20 mg that demonstrates comparative bioavailability of Tadalafil Chewable Tablets 20 mg to Cialis Tablets 20 in the fasted state and the absence of a food effect between Tadalafil Chewable Tablets 20 mg (fed vs. fasted). Sponsor has also demonstrated bioequivalence fasting subjects taking Tadalafil Chewable Tablets with and without water. This demonstration of comparative bioavailability indicates that the benefit of Tadalafil Chewable Tablets is comparable to the benefit of the reference product, Cialis Tablets.

8. Review of Safety

8.1. Safety Review Approach

The Clinical review team conducted a review of all safety information generated in the Sponsor's four single-dose, relative BA/BE clinical studies. We also conducted a review of tadalafil postmarketing safety experience information. As this NDA was submitted as a 505(b)(2) application, some subsections of this Clinical Review template are not applicable and are omitted.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The safety database consists of a total of 94 subjects who received at least one dose of Tadalafil Chewable Tablets and 73 received at least one dose of Cialis tablets. Of these, 17 received an initial Tadalafil Chewable formulation in Study 079. The remaining subjects received the to-be-marketed (TBM) Tadalafil Chewable Tablets. Subjects were all healthy, young, Asian males. The duration of exposure in each arm of the BE studies was single dose only.

Table 25: NDA 218527 Safety Database

Study	Enrolled/ Completed	Test Product Fasted	Test Product Fed	Ref Product Fasted
079	18/16	17	16	18
008	14/13	13		14
051	42/37	40	39	41
023	24/21	24	22	

Source: Sponsor's CSRs of respective clinical pharmacology studies

8.2.2. Relevant characteristics of the safety population

Demographics for the relative BA/BE studies submitted in this NDA were presented in the individual study report analyses. Overall, subjects were generally healthy, young, Asian male volunteers.

8.2.3. Adequacy of the safety database

The safety database is adequate for this bioequivalence-based 505(b)(2) application. The Sponsor cited and presented information on the extensive experience with the reference product, Cialis as well as referencing the approved product prescription and patient labeling.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The Sponsor's assessment of adverse events appears to be adequate.

8.3.2. Categorization of Adverse Events

See information in Section 8.4.

8.3.3. Routine Clinical Tests

The safety assessment methods and time points for collection of adverse events, vital signs, oro-mucosal assessments, and clinical laboratories are adequate. It is noted that for each treatment arm, subjects were in-clinic and had frequent vital signs determinations that would permit frequent interaction with study staff to allow prompt observation and reporting of any adverse events.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in any of the studies submitted in this NDA.

8.4.2. Serious Adverse Events

There were no serious adverse events in any of the submitted studies in this NDA.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

In Study TADA-23-023, one subject (b) (6) "vomited before 2 times of median Tmax of the investigational product in one period and was withdrawn from study." The subject vomited post-dose in period 1 (Tadalafil Chewable Tablets dosed with water) at a time point that did not permit determination of Tmax for this subject. Subject was withdrawn from study.

> *Reviewer's Comment: This event was a single episode of post-dose vomiting for the test product and does not raise a new safety concern*.

In TADA-21-079, Subjects (b) (6) failed to report for period 3 and were discontinued. No additional information was provided in their CRFs.

In TADA-22-008, Subject (b) (6) withdrew consent for period 1. No additional information was provided in his CRF.

In TADA-22-051, Subject (b) (6) did not report for periods 2 and 3. Subject (b) (6) did not report for period 2. No additional information was provided in their CRFs.

In TADA-23-023, Subjects (b) (6) withdrew consent for periods 1 and 2. No additional information was provided in their CRFs

Significant Adverse Events

There was no significant adverse event reported in any of the 4 studies provided in this NDA that would raise concerns that this proposed product will have a different safety profile when compared to the approved tadalafil tablet.

8.4.4. Treatment Emergent Adverse Events and Adverse Reactions

There were 2 clinical adverse events in the clinical trial results submitted in this NDA. Subject TADA-23-023, in Study 023, experienced 1 episode of vomiting that occurred following dosing of 20 mg Tadalafil Chewable Tablets with water in a fasting state. Subject (b) (6) in TADA-22-051 had an episode of pyrexia. The remaining adverse events were laboratory-related adverse events and are discussed in Section 8.45 below.

8.4.5. Laboratory Findings

In this section, all laboratory-related adverse events reported in the Sponsor's 4 relative BA/Be studies are described and discussed. Table 26 presents a clinical summary of these events.

Table 26: NDA 218527 Laboratory Adverse Events for Studies Submitted in NDA

Study # Design	Subj #	AE	ONSET	Last dose received/ Doses received	End-of-study (EOS) lab date	Medications	Medical History
TADA-21-079 **Tfed (A)** **Tfasted (B)** **Rfasted (C)**							
	(b) (6)	Bili conjugated increased	(b) (6) EOS	(b) (6) ref fasted/ test fed/ ref	(b) (6)	No	None
		Hgb decreased	(b) (6) EOS	(b) (6) ref fasted/ all 3 doses		No	None
TADA-22-051 **Tfed (A)** **Tfasted (B)** **Rfasted(C)**							
	(b) (6)	Hgb decreased	(b) (6) EOS	(b) (6) ref fasted/ all 3 doses	(b) (6)	No	None
		Hgb decreased	(b) (6) EOS	(b) (6) test fed/ all 3 doses		No	None
		Hgb decreased	(b) (6) EOS	(b) (6) test fed/ all 3 doses		No	None
		Eosinoph increased	(b) (6) EOS	(b) (6) test fed/ all 3 doses		No	None
		Eosinoph increased	(b) (6) EOS	(b) (6) test fed/ all 3 doses		No	None
		AST increased	(b) (6) EOS	(b) (6) ref fast/ all 3 doses		No	None
		ALT increased	(b) (6) EOS	(b) (6) ref fed/ all 3 doses		No	None
		ALT increased	(b) (6) EOS	(b) (6) test fed/ all 3 doses		No	None
		ALT increased	(b) (6) EOS	(b) (6) test fast/ all 3 doses		No	None
		Pyrexia	(b) (6) EOS	(b) (6) test fast/ all 3 doses		No	None
TADA-22-008 **R fasted** **T fasted**							

	(b) (6)	ALT increased	(b) (6) EOS	(b) (6) ref/ test and reference	(b) (6)	No	None
		AST increased	(b) (6) EOS	(b) (6) ref/ test and reference		No	None
TADA-23-023 all arms fasting without water (A) with water (B)							
	(b) (6)	Vomiting	(b) (6) 4.5 hr p dose	(b) (6) received test B			none
		Glucose increased	(b) (6) EOS	(b) (6) without water/ both treatments	(b) (6)	No	None, glucose 138 at study entry
		Glucose increased	(b) (6) EOS	(b) (6) without water/ both treatments		No	None, glucose 84 at study entry
		ALT increased	(b) (6) EOS	(b) (6) without water/ both treatments		No	None

T=test R=ref; test dose = Tadalafil Chewable Tablet 20 mg, ref = Cialis 20 mg; EOS=end-of-study
Sources: Clinical reviewer overview based on:

- Subject medications and medical history from CSR datasets.
- Concomitant medication from CSR datasets
- Treatment received and last treatment received from CSR datasets: Table 23 TADA-22-051, Tables 17 and 24 TADA 23-023, Table 15 TADA-22-008, TADA-22-079. Tables 9 in CSR TADA TADA-23-023, Tables 7 and 18, CSR TADA-22-008, Tables 7 and 16, TADA-22-008, and TADA-022-079 Tables 8 and 20.

Eighteen adverse events were reported in 16 subjects. Two of the adverse events (in 2 subjects) were clinical events. Sixteen adverse events (in 14 subjects) were laboratory events, all reported at end of study. The last treatment taken for 9 of the 16 lab adverse events was test product, while last treatment in 7 of 16 were reference product. As laboratory testing was performed at screening and end of study, attribution to a particular treatment is confounded.

Table 27 below, derived from the Sponsor's Integrated Summary of Safety (ISS), summarizes the clinical and laboratory adverse events from all 4 studies.

Table 27: Summary of TEAE by SOC and MedDRA PT

System Organ Class (SOC) MedDRA Preferred Term	TADA-21-079 20 mg (18)	TADA-22-008 20 mg (14)	TADA-22-051 20 mg (42)	TADA-23-023 20 mg (24)	Overall 20 mg (98)
Investigations					
Alanine aminotransferase increased		1[a][c]	3[a][c]	1[a][b][c]	5
Aspartate aminotransferase increased		1[a][c]	1[a][c]		2
Hemoglobin decreased	1[a]		3[a][b]		4
Eosinophil count increased			2[a][b]		2
Blood glucose increased				1[a][d]	1
Bilirubin conjugated	1[a][b][c]				1
General disorders and administration site conditions					
Pyrexia			1[b][c]		1
Gastrointestinal disorders					
Vomiting				1[c][f]	1

a = Post-study adverse events; b = Not attributed to a particular treatment; c = possibly related to treatment; d = not related to treatment; e = adverse event treated; f = Tadalafil Chewable Tablets 20 mg Fasted with water, SOC: System Organ Class; MedDRA: Medical Dictionary for Regulatory Activities; ( ): sample size; TEAE: Treatment-emergent AEs (TEAEs) are defined as AEs that are new onset or increase in severity after first dosing.

Source: TADA-21-079 CSR; TADA-22-008 CSR; TADA-22-051 CSR and TADA-23-023 CSR.

Source: Clinical reviewer derived from a Snapshot of Table 9 Integrated Summary of Safety Narratives for Laboratory Adverse Events

All enrolled subjects in the Phase 3 studies were healthy young males who had no identified underlying conditions or diseases at the screening assessment. However, testing at screening was not done for hepatitis. In addition, laboratory abnormalities noted at Screening could be determined by the clinical investigator to be not clinically significant which could allow study entry of subjects with pre-existing conditions such as hepatitis B.

Case narratives below were abstracted from subject CRFs. In addition, case narratives for laboratory adverse events were requested from Sponsor in the 74-Day Letter and were submitted on December 15, 2023. In this section of the review, each narrative is individually assessed with a special focus on possibly confounding background conditions and potential for drug causality.

a) Abnormal Liver Function Tests (n=6 subjects)

1) TADA-21-079 (b) (6) Subject is a 30-year-old male who weighs 59 kilos and has BMI of 19.27 kg/m^2. He is a healthy adult male with a negative medical history, taking no medications and no history of drug or alcohol abuse. At screening ((b) (6)), his temperature was 98.1 F and his blood pressure (BP) was 120/80 mmHg. No findings of icterus were noted on physical examination. His hemoglobin was 13.6 gm% and his total RBC count was 5.13 million cells/cm^3. His direct bilirubin was 0.61 mg/dl (normal up to 0.3 mg/dl) and his total bilirubin was 1.6 mg/dl (normal 0.3-1.2mg/dl). Urine bilirubin and urobilinogen were within normal limits. His baseline SGOT was 23.0 U/L (normal < 40) and SGPT was 29 U/L (normal <45). The alkaline phosphatase was 72.0 (normal range 40-129). Repeat bilirubin determinations (b) (6)) showed that his direct bilirubin was 0.27 mg/dl (nl up to 0.3 mg/dl) and his total bilirubin was 0.62 mg/dl (normal 0.3-1.2mg/dl). Liver enzymes were not repeated. The subject did not report to the study facility for period 3 and was withdrawn from this period ((b) (6) Repeat bilirubin determinations (on (b) (6)) showed direct bilirubin 0.65 mg/dl (nl up to 0.3 mg/dl) and total bilirubin 1.47 mg/dl (normal 0.3-1.2mg/dl). His liver enzymes were SGOT 28.0 U/L, SGPT 30.0 U/L and alkaline phosphatase 70.0 U/L. His bilirubin determinations were repeated on (b) (6) and showed direct bilirubin 0.3 mg/dl (nl up to 0.3 mg/dl) and total bilirubin 1.34 mg/dl (normal 0.3-1.2mg/dl). His SGPT was 15.0 U/L and his alkaline phosphatase was 69.0 U/L. The last dose of any study drug was the reference drug take during a fasted state on (b) (6) (b) (6)

Subject (b) (6) - overview

Period 2	**Period 3**
(b) (6) Cialis 20 mg	(b) (6) Not Dosed

Screening (b) (6)	**Follow-up** (b) (6)	**Follow-up** (b) (6)	**Follow-up** (b) (6)
Direct bilirubin, total bilirubin (mg/dL)			
0.6, 1.6	0.27, 0.62	0.65, 1.47	0.3, 1.34

Reviewer's Comment: The subject's baseline serum bilirubin improved after the study and worsened when tested during follow-up. After review of the laboratory data (i.e. time sequence of bilirubin determinations, timing of the last dose of study drug, and baseline bilirubin levels), it appears that subject's bilirubin changes were variable and the clinical reason for these changes is unknown. The Sponsor and Clinical review team agree that the elevated follow-up serum bilirubin does not appear to be related to use of study drug.

2) TADA-22-051 (b) (6): Subject is a 35-year-old male who weighs 77 kilos and has a BMI of 29.71 kg/m². He is a healthy adult male with a negative medical history, taking no medications and no history of drug or alcohol abuse. At screening, on (b) (6), his temperature was 98.1 F and his blood pressure was 120/80 mmHg. His SGOT was 39.0 U/L (normal <40) and his SGPT was 55.0 U/L (normal <45). This lab abnormality was noted. The subject's urinalysis was normal. At screening, his BUN was 13.0 mg/dl and his creatinine was shown as 0.0 mg/dl. On (b) (6), his SGOT was 64.0 U/L which was elevated, and his SGPT was 149.0 U/L which was elevated. His alkaline phosphatase was 113.0 U/L (normal 49-210), while at screening, his alkaline phosphatase was 78.0 U/L. His BUN was 11.0 mg/dl and his creatinine was 0.86 mg/dl. The subject's SGOT/SGPT values were elevated (as reported in the Sponsor's CRF). On (b) (6), his SGPT was 28.0 U/L. Follow up SGOT of 60.0 U/L and SGPT of 79.0 U/L were obtained on (b) (6). The subject received all three treatments and last study drug dose was on (b) (6). The final treatment in Period 3 was the reference product under fasting conditions.

Subject (b) (6) - overview

Doses of Study Drug	**Period 1** (b) (6) Test Product Fed	**Period 2** (b) (6) Test Product Fasting	**Period 3** (b) (6) Reference Fasting
Screening (b) (6)	**End of Study** (b) (6)	**Follow-up** (b) (6)	**Follow-up** (b) (6)
SGOT/SGPT (UL)			
39/55	64/149	28/60	60/79

Reviewer's Comment: The subject entered the study with a high-normal SGOT (39 UL, normal <40) and an elevated SGPT (55 U/L, normal <45). At end-of-study, both his SGOT (64 U/L) and SGPT (149 U/L) were elevated and increased from baseline laboratory assessments. On first follow-up, both his SGOT and SGPT had decreased (20 U/L and 60 U/L, respectively. However, on second follow-up, his SGOT and SGPT was again increased (60 U/L and 79 U/L, respectively). Based on the evidence, it appears that the subject's SGOT and SGPT are variable with the reason for these elevations unknown. The Sponsor and Clinical review team agree that the elevated SGOT and SGPT levels do not appear to be related to use of study drugs.

3) TADA-22-051 (b) (6): Subject is a 41-year-old male who weighs 64 kilos and has a BMI of 23.23 kg/m². He is a healthy adult male with a negative medical history, taking no medications with no history of alcohol or drug abuse. At Screening ((b) (6)), his temperature was 97.8 F and his blood pressure was 110/76 mmHg. His SGOT was 44.0 U/L (normal <40) and his SGPT was 60.0 U/L (normal <45). Both were noted to be increased. His alkaline phosphatase was 123.0 U/L, which was normal. His urinalysis was normal. On (b) (6), the subject's SGOT was 30.0 U/L and his SGPT was 74.0 U/L, which was again elevated. His alkaline phosphatase was 117.0 U/L (normal 49-210). His direct bilirubin was 0.31 mg/dl (normal up to 0.30). A follow-up SGPT on (b) (6) was 38.0 U/L. The subject received all three study treatments and last dose of study drug was for the test product under fed conditions on (b) (6).

Subject (b) (6) - overview

Doses of Study Drug	**Period 1** (b) (6) Test Product Fasting	**Period 2** (b) (6) Reference Fasting	**Period 3** (b) (6) Test Product Fed
Screening (b) (6)	**End of Study** (b) (6)	**Follow-up** (b) (6)	
SGOT/SGPT (U/L)			
44/60	30/74	SGPT 38	

Reviewer's Comment: The subject entered the study with elevated SGOT (44 U/L, normal < 40) and elevated SGPT (60 U/L, normal < 45). At end-of-study, his SGOT was in the normal range (30 U/L) and his SGPT had increased modestly (74 U/L). A follow-up SGPT was in the normal range and below his baseline level (38 U/L). Based on the evidence, it appears that the subject's SGOT and SGPT are variable with the clinical reason unknown. The Sponsor and Clinical review team agree the elevated serum SGPT does not appear to be related use of study drugs.

4) TADA-22-051 (b) (6): Subject is a 35-year-old male who weighs 62 kilos and has a BMI of 29.92 kg/m². There is no history of drug or alcohol use. He is a healthy adult male with a negative medical history and taking no medications. At Screening ((b) (6)), his temperature was 98.1 F and his blood pressure was 110/76 mmHg. His SGOT was 32.0 U/L (normal <40) and his SGPT was 44.0 U/L (normal <45). His urinalysis was normal. On (b) (6) (b) (6), the subject's SGOT was 39.0 U/L and his SGPT was 75.0 U/L, which was elevated. His alkaline phosphatase was 103.0 U/L (normal 49-210). A follow-up SGPT on (b) (6) (b) (6) was 28.0 U/L. The subject received all three treatment doses and the last dose of study drug was the test product under fasting conditions on (b) (6).

Subject (b) (6) - overview

Doses of Study Drug	**Period 1** (b) (6) Reference Fasting	**Period 2** (b) (6) Test Product Fed	**Period 3** (b) (6) Test Product Fasting
Screening (b) (6)	**End of Study** (b) (6)	**Follow-up** (b) (6)	
SGOT/SGPT (U/L)			
32/44	39/75	SGPT 28	

Reviewer's comment: The subject entered the study with a high-normal SGPT (44 U/L, normal <45). At end-of-study, his SGPT had increased modestly (75 U/L). A follow-up SGPT (28 U/l) was lower than his baseline value and within the normal range. Based on the evidence, it appears that the subject's SGPT is variable, for unknown reasons. This event could reflect normal lab variability or could be due to some other factor(s). The Sponsor and Clinical review team agree that the elevated SGPT does not appear to be related to the study drugs.

5) TADA-22-008 (b) (6): Subject is a 29-year-old male who weighs 59 kilos and has a BMI of 20.90 kg/m². He is a healthy adult male with a negative medical history, taking no medications and no history of alcohol or drug abuse. At Screening (b) (6)), his temperature was 96.5 F and his blood pressure was 130/80 mmHg. His SGOT was 32.0 U/L (normal <40) and his SGPT was 44.0 U/L (normal <45). His urinalysis was normal. On (b) (6) (b) (6), his SGOT was 68.0 U/L and his SGPT was 78.0 U/L which were both elevated. His alkaline phosphatase was 53.0 U/L (normal 49-210). His follow-up SGOT/SGPT values on (b) (6) were 24.0 U/L and 27.0 U/L, respectively, which were within normal limits. His last dose of study drug was for the test product under fasting conditions on (b) (6) (b) (6) He received two drug doses with the final dose being the reference product on (b) (6) (b) (6)

Subject (b) (6) - overview

Doses of Study Drug	**Period 1** (b) (6) Test Product Fasted	**Period 2** (b) (6) Reference fasted
Screening (b) (6)	**End of Study** (b) (6)	**Follow-up** (b) (6)
SGOT/SGPT (U/L)		
32/44	68/78	24/27

Reviewer's comment: The subject entered the study with a high-normal SGPT (44 U/L, normal 45). At end-of-study (performed more than 2 months after his last dose of study drug), his SGOT and SGPT were elevated outside the normal range (68 U/L and 78 U/L, respectively). At follow-up, his SGOT (24 U/L) and SGPT (27 U/L) had returned to the normal range and were lower than his baseline values. Based on the evidence, it appears that the subject's serum SGOT and SGPT were variable, with no clinical reason identified. This event could reflect normal lab variability or other factor(s) external to the trial. The Sponsor and the Clinical review team agree that these elevated liver function tests do not appear to be related to use of the study drugs.

6) TADA-23-023 (b) (6): Subject is a 29-year-old male who weighs 91 kilos and has a BMI of 29.71 kg/m². He is a healthy adult male with a negative medical history, taking no medications and no history of alcohol or drug abuse. At screening (b) (6)), his temperature was 98.1 F and his blood pressure was 120/80 mmHg. His SGOT was 47.0 U/L (normal <40) and his SGPT was 74.0 U/L (normal <45). His alkaline phosphatase was 49.0 U/l which was normal. His urinalysis was normal. On (b) (6), a repeat SGPT prior to any drug administration was still elevated at 64.0 U/L. On (b) (6). The subject's SGOT was 36.0 U/L and his SGPT was 83.0 U/L. His alkaline phosphatase was 50.0 U/L (normal 49-210). His direct bilirubin was 0.31 mg/dl (normal up to 0.30) and his alkaline phosphatase was 50.0 U/L. His follow-up SGPT on (b) (6) was 57.0 U/L. The subject's last dose of study drug was for the test product under fed conditions on (b) (6) (b) (6). The subject received all 2 study doses with the last study drug dose administered on (b) (6).

Subject (b) (6) - overview

Doses of Study Drug	**Period 2** (b) (6) Test Product with water		
Screening (b) (6)	**Repeat** (b) (6)	**End of Study** (b) (6)	**Follow-up** (b) (6)
SGOT/SGPT (U/L)			
47/74	SGPT 64	36/83	SGPT 57

Reviewer's Comment: The subject entered the study with elevated SGOT (47 U/L, normal < 40) and elevated SGPT (74 U/L and 64 U/L, normal < 45). At end-of-study, his SGOT was decreased (36 U/L) and his SGPT had increased modestly (83 U/L). In follow-up, his SGPT was still above the normal range, but had decreased to a level (57 U/L) below his baseline values. After review, it appears the subject's SGOT and SGPT were variable for reasons unknown. The Sponsor and Clinical review team agree that these elevated SGPT results do not appear to be related to use of study drugs.

Table 28: Summary of Elevated SGOT/SGPT results reported in the 4 completed clinical studies submitted in support of tadalafil chewable tablets

Subject	Baseline SGOT/SGPT (U/L)	End of Study SGOT/SGPT (U/L)	Follow-up SGOT/SGPT (U/L)	Comments*
TADA-22-051 (b) (6)	39/55	64/149	#1: 28/60 #2: 60/79	• Baseline elevated SGPT • Baseline 'high-normal' SGOT • EOS both increased • Follow-up levels decreased then increased, both still elevated.
TADA-22-051 (b) (6)	44/60	30/74	38 SGPT	• Baseline elevated SGOT and SGPT • EOS SGPT increased • Follow-up SGPT decreased to below baseline
TADA-22-051 (b) (6)	32/44	39/75	28 SGPT	• Baseline normal SGOT and 'high-normal' SGPT • EOS both increased. SGPT to abnormal range • Follow-up SGPT decreased to below baseline
TADA-22-008 (b) (6)	32/44	68/78	24/27	• Baseline normal SGOT and 'high-normal' SGPT • EOS (2 months after last dose) both increased to abnormal range • Follow-up SGOT and SGPT decreased to below baseline
TADA-23-023 (b) (6)	47/74 (repeat SGPT 64)	36/83	57 SGPT	• Baseline elevated SGOT and SGPT • EOS SGPT increased • Follow-up SGPT decreased but still elevated.

**Abbreviations: EOS = End of Study*
Source: Data obtained from the Sponsor's CSRs submitted in NDA 218527

Reviewer's Summary Comment: As summarized in Table 28, the identified elevated transaminases reported in these 5 cases do not appear to be related to the study drugs. The reader is referred to the individual Reviewer's Comments on each of the 6 case narratives above. Overall, the laboratory evidence does not indicate a drug effect on liver function tests and does not raise new safety concerns or trends. These cases include subjects with elevated or high-normal liver function tests at baseline, modest increases of liver function tests in most subjects, follow-up liver function tests that decreased then increased, and follow-up liver function tests that decreased to below the subject's baseline. Of note, there were 9 additional subjects with elevated SGOT, SGPT, or both, at baseline, in whom subsequent liver function tests were not elevated. The reasons for the changes in liver function tests are unknown, but could include baseline abnormalities, liver function test variability in the study populations, intercurrent factors, or other unknown factors.

b) Decreased Hemoglobin (n=4)

1) TADA-21-079 (b) (6) Subject is a 30-year-old male who weighs kilos and has a BMI of 27.10 kg/m^2. He is a healthy adult male with a negative medical history, taking no medications with no history of alcohol or drug use. At Screening ((b) (6)), his temperature was 98.5 F and his blood pressure was 104/70 mmHg. His hemoglobin was 11.2 gm% (normal range 12.0-18.0). His total RBC count was 4.53 million cells/cm^3 (normal range 4.0-6.0). His urinalysis at screening was negative. On (b) (6), at end-of-study, his hemoglobin was 10.4 gm% and his total RBC count was 4.35 million cells/cm^3. The subject's last dose of study drug (reference drug fasting) was on (b) (6). The subject received all 3 study doses. A follow-up hemoglobin on (b) (6), was 11.9 gm%.

Subject (b) (6) - overview

Doses of Study Drug	**Period 1** (b) (6) Test Product Fed	**Period 2** (b) (6) Test Product Fasting	**Period 3** (b) (6) Reference Fasting
Screening (b) (6)	**End of Study** (b) (6)	**Follow up** (b) (6)	
Hemoglobin gm%			
11.2	10.4	11.9	

Reviewer's Comment: The subject's hemoglobin levels were below the normal range at Screening, decreased modestly at end-of-study, and improved at follow-up approximately 3 months later, yet remained below the normal range for male subjects. From a clinical perspective, research identified a normal range for hemoglobin for adult males in India of 12.3 to 17 gm/dl for the 95% reference distribution (Indian J Clin Biochem, 2014 Jul;29(3):290-7: The Lancet Global Health, 2019(7) 12; pages e1683-e1694: Anaemia among men in India: a nationally representative cross-sectional study; Didzun O, Jan-

Walter De Neve Scd et. al.). As the hemoglobin level in this subject was low at baseline, a causal relationship with use of the study drugs is unlikely.

2) TADA-22-051 (b) (6): Subject is a 38-year-old male who weighs 78 kilos and has a BMI of 29.00 kg/m². He is a healthy adult male with a negative medical history and taking no medications. At Screening ((b) (6)), his temperature was 97.9 F and his blood pressure was 130/90 mmHg. His hemoglobin was 11.4 gm% (normal 12.0-18.0) and his total RBC count was 5.47 million cells/cm^3. His urinalysis was normal. On (b) (6), at end-of-study, his hemoglobin was 10.4 gm% (normal 12.0-18.0) and his total RBC count was 5.10 million cells/cm^3. Follow-up hemoglobin on (b) (6) was 13.1 gm%. The subject received all 3 study doses. The last dose he received was the reference drug on (b) (6) (b) (6).

Subject (b) (6) - overview

Doses of Study Drug	**Period 1** (b) (6) Test Product Fed	**Period 2** (b) (6) Test Product Fasting	**Period 3** (b) (6) Reference Fasting
Screening (b) (6)	**End of Study** (b) (6)	**Follow-up** (b) (6)	
Hemoglobin gm%			
11.4	10.4	13.1	

Reviewer's Comment: The subject's hemoglobin was below the normal range at Screening, decreased modestly at end-of-study, then improved to the normal range at follow-up. This case is confounded by the subject's baseline anemia and appears unlikely to be related to use of study drugs.

3) TADA- 22-051 (b) (6): Subject is a 45-year-old male who weighs 71 kilos and has a BMI of 29.72 kg/m². He is a healthy adult male with a negative medical history and taking no medications. At screening ((b) (6)), his temperature was 97.8 F and his blood pressure was 130/90 mmHg. His hemoglobin was 11.0 gm% (normal 12.0-18.0) and his total RBC count was 5.09 million cells/cm^3. He also had 76% polymorphonucleocytes (normal 35-75) and 18 % lymphocytes (normal 20-45%). His urinalysis was normal. On (b) (6), at end-of-study, his hemoglobin was 10.3 gm% with normal percentages of polymorphonucleocytes and lymphocytes. Follow-up hemoglobin value obtained on (b) (6) (b) (6) was 10.7 gm%. The subject received all three treatments with the subject's last dose of study drug on (b) (6).

Subject (b) (6) - overview

Doses of Study Drug	Period 1 (b) (6) Test Product Fasting	Period 2 (b) (6) Reference Fasting	Period 3 (b) (6) Test Product /Fed
Screening (b) (6)	**End of Study** (b) (6)	**Follow-up** (b) (6)	
Hemoglobin gm%			
11.0	10.3	10.7	

Reviewer's Comment: The subject's hemoglobin was below the normal range at Screening, decreased modestly at end-of-study, and improved modestly at follow-up, yet remained below the normal range. This case is confounded by the subject's baseline anemia and does not appear to be related to use of study drugs.

4) *TADA-22-051* (b) (6): Subject is a 37-year-old male who weighs 77 kilos and has a BMI of 29.34 kg/m². He is a healthy adult male with a negative medical history and on no medications. At screening ((b) (6)) his temperature was 97.8 F and blood pressure was 130/90 mmHg. Cardiomegaly was noted on chest x-ray. The subject denied shortness of breath, dyspnea, fatigue, and his ECG was normal. His hemoglobin was 11.3 gm% (normal 12.0-18.0) and his total RBC count was 5.45 million cells/cm^3. His urinalysis was normal. At end-of-study ((b) (6)), his hemoglobin was 10.4 gm% and his total RBC count was 5.13 million cells/cm^3. His end-of-study direct bilirubin was 0.32 mg/dl (normal up to 0.3). At screening, his direct bilirubin was 0.21 mg/dl. The subject's lowered hemoglobin was noted by the clinical investigator and a follow-up determination was ordered. On (b) (6) (b) (6), the subject's final hemoglobin value was 11.2 gm%. The subject received all three study treatments and was administered the test product under fed conditions as the last study dose on (b) (6).

Subject (b) (6) - overview

Doses of Study Drug	Period 1 (b) (6) Test Product Fasting	Period 2 (b) (6) Reference Product Fasting	Period 3 (b) (6) Test Product Fed
Screening (b) (6)	**End of Study** (b) (6)	**Follow-up** (b) (6)	
Hemoglobin gm%			
11.3	10.4	11.2	

Reviewer's comment: The subject's hemoglobin was below the normal range at Screening, decreased modestly at end-of-study, and improved modestly at follow-up, yet

remained below the normal range. This case is confounded by the subject's baseline anemia but does not appear to be causally related to use of study drugs.

Table 29: Summary of low hemoglobin results reported in the 4 completed clinical studies submitted in support of tadalafil chewable tablets

Subject	Baseline (BL) Hemoglobin in gm%	End-of-Study (EOS) Hemoglobin	Follow-up (FU) Hemoglobin	Comments*
TADA-21-079 (b) (6)	11.2	10.4	11.9	• BL: Hgb low • EOS: Hgb decreased • FU: Hgb increased, but still below normal range
TADA-22-051 (b) (6)	11.4	10.4	13.1	• BL: Hgb low • EOS: Hgb decreased • FU: Hgb increased into normal range
TADA-22-051 (b) (6)	11.0	10.3	10.7	• BL: Hgb low • EOS: Hgb decreased • FU: Hgb increased, but still below normal range
TADA-22-051 (b) (6)	11.3	10.4	11.2	• BL: Hgb low • EOS: Hgb decreased • FU: Hgb increased, but still below normal range

**BL = baseline, EOS = end of study, FU = follow up*
Sources: Data obtained from CSRs in the Sponsor's NDA 218527

Reviewer's Summary Comment: In all 4 cases reported above, the baseline hemoglobin level was below the normal range and decreased modestly by the end-of-study blood draw. In all 4 cases, the hemoglobin increased on follow-up, but remained below the normal range in 3 of the 4 cases. Of note, 6 additional subjects had hemoglobin below the normal range at Screening (range 10.8 to 11.8) and none of these subjects had a low hemoglobin at end-of-study. No subject with a hemoglobin of 12 or greater at Screening had a low hemoglobin at end-of-study. The clinical reason for these baseline low hemoglobin values is unclear, but it is unlikely that the reported changes in values are related to treatment study drugs.

c) Blood Glucose Increases (n=2)

1) TADA-23-023 (b) (6): Subject is a 33-year-old male who weighs 69 kilos and has a BMI of 23.60 kg/m². He is a healthy adult male with a negative medical history and taking no

medications(s). At Screening ([(b) (6)]), his temperature was 98.1 F and his blood pressure was 130/80 mmHg. His random blood glucose was 138 mg/dl (normal < 140 mg/dl) at 11:49 am. No other significant laboratory abnormalities were detected. His urinalysis was normal with no glucose detected. The subject received his last dose of study drug (test product fasting) on [(b) (6)]. At end-of-study, on [(b) (6)], at 7:44 am, he had a random glucose of 226 mg/dl. A follow-up blood glucose test was ordered. The subject received both study doses (test product fasting with and without water). A random blood glucose performed on [(b) (6)], at 10:56 am, was 167 mg/dl.

Reviewer's Comment: Blood glucose can vary widely during the day. No information is available regarding relationship of the random blood glucose tests to meals or other food ingestion or to activities. The subject's random glucose on follow-up was elevated. Causality between the study drugs and the subject's random blood glucose increases cannot be assessed but does not appear to be related to study drug use.

2) TADA-23-023 [(b) (6)]: Subject is a 41-year-old male who weighs 71 kilos and has a BMI of 27.73 kg/m². He is a healthy adult male with a negative medical history and taking no medications(s). At Screening ([(b) (6)]), his temperature was 98.1 F and his blood pressure was 110/78 mmHg. His random glucose test was 84 mg/dl (normal up to 140) at 12:17 pm. His total cholesterol was 300 mg/dl and his SGOT was 44.0 U/L. His urinalysis was normal. At end-of-study, on [(b) (6)], at 7:44 am, his random blood glucose was 170 mg/dl. His serum cholesterol was 301 mg/dl and his SGPT was 54.0 U/L. The investigator requested follow up for the elevated blood glucose. The requested follow up was not in the CRF. At FDA's request, a follow-up blood glucose was sought from the subject's local physician; however, a follow-up blood glucose result was not received.

Reviewer's Comment: Blood glucose can vary widely during the day. No information is available regarding relationship of the random blood glucose tests to meals or other food ingestion or to activities. Causality between the study drugs and the subject's random blood glucose increases cannot be assessed but does not appear to be related to study drug use.

Reviewer's Summary Comment: Without specific information on food intake and activities, it is not possible to assess the clinical reason for increased blood glucose values. However, these two cases do not support that there is any causality between increased blood glucose and use of study drugs.

Reviewer's Summary Comments on abnormal laboratory results:

- *Abnormal labs were relatively common at baseline. Baseline liver function tests were either increased, or hemoglobin decreased, in 22 of 91 (24%) total subjects.*
    - *11 subjects had baseline elevated liver enzymes*
    - *1 subject had increased bilirubin at baseline*
    - *10 subjects had hemoglobin below 12 at baseline*

- *The Sponsor reported 10 subjects had laboratory adverse events of 'abnormal liver function tests' (n=6) or 'decreased hemoglobin' (n=4) based on end-of-study lab assessments.*

- *Of the 6 subjects with abnormal liver function test events:*
  - *1 had elevated bilirubin at baseline*
  - *3 had elevated liver enzymes at baseline, and*
  - *2 had high-normal (just below the limit for elevated) liver enzymes at baseline*

- *Of the 6 subjects with abnormal liver function test events:*
  - *The subject with elevated bilirubin at baseline still had elevated bilirubin on follow-up.*
  - *Of the 5 subjects with elevated liver enzymes at baseline, on follow-up*
    - *1 still had elevated liver enzymes*
    - *4 had liver enzymes below their baseline values.*

- *Of the 2 subjects with high-normal liver enzymes at baseline in whom abnormal liver function test events were reported, their end-of-study liver enzyme elevations were minimal.*

- *All 4 subjects with decreased hemoglobin events had low hemoglobin at baseline.*
  - *3 of the 4 subjects still had hemoglobin below the normal range on follow-up.*
  - *No subject with a normal baseline hemoglobin had an adverse event of decreased hemoglobin at end-of-study.*

Taken together, the clinical review team concludes that this evidence does not suggest a causal relationship between any of these lab adverse events and use of study drugs. Instead, it appears that laboratory abnormalities at baseline, lab results variability, study design issues (e.g., outpatient setting, time between dosing) and other unknown factors, may have played a role in these abnormal laboratory results. Further, without pre-specification of lab abnormalities of clinical significance (e.g., liver enzymes > 2-fold increase, >5-fold increase, etc), it is difficult to classify the lab abnormalities as clinically significant adverse events.

8.4.6. Vital Signs

One episode of pyrexia was reported as a vital sign abnormality. This report was not temporally related to test or reference product dosing and resolved in one day. Otherwise, no notable vital signs changes were reported or identified upon review of this submission.

8.4.7. Electrocardiograms (ECGs)

There were no notable ECG findings.

8.4.8. QT

There were no notable QT findings reported in the studies and a tQT study was not required for this 505(b)(2) NDA submission.

8.4.9. Immunogenicity

This submission is not for a biologic product or peptide and no data on immunogenicity was required.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Oro-mucosal Irritation

At the request of FDA, the Sponsor assessed the potential for oral mucosal irritation in Studies TADA-22-051 and TADA-23-023.

In TADA-22-051, the following oro-mucosal evaluations were performed:

Following ingestion of Tadalafil Chewable Tablets 20 mg Fed (Treatment A), Tadalafil Chewable Tablets 20 mg Fasted (Treatment B), and Cialis Tablets 20 mg Fasted (Treatment C), mucosal irritation assessments was completed by the subject (collected by a study physician) within 40 minutes prior to dosing (00.00 hour) and at 00.50, 01.00 and 12.00 hours of post-dose in each period (±10 minutes). Tadalafil Chewable Tablets were chewed, and Cialis Tablets were ingested intact, each with 240 mL of water at ambient temperature.

Subject self-reports were assessed using a 10-point (0-9) scale for (i) Itching; (ii) Burning Sensations; (iii) Difficulty Swallowing; and (iv) Taste Changes. None of the mucosal irritation parameter results were considered adverse events. For all variables during Tadalafil Chewable Tablets 20 mg *Fed*, Tadalafil Chewable Tablets 20 mg *Fasted* and Cialis Tablets 20 mg *Fasted*, the mean score ranged from 0.00 to 0.08, with no significant treatment differences.

In TADA-23-023, the following oro-mucosal evaluations were performed:

Following ingestion of Tadalafil Chewable Tablets 20 mg Fasted and Without Water (Treatment A) and Tadalafil Chewable Tablets 20 mg Fasted and With Water (Treatment B), mucosal irritation assessments was completed by the subject (collected by a study physician) within 40 minutes prior to dosing (00.00 hour) and at 00.50, 01.00 and 12.00 hours of post-dose in each period (±10 minutes).

Subject self-reports were assessed using a 10-point (0-9) scale for (i) Itching; (ii) Burning Sensations; (iii) Difficulty Swallowing; and (iv) Taste Changes. None of the mucosal irritation parameter results were considered adverse events. For all variables during Tadalafil Chewable Tablets 20 mg *Fasted and Without Water* (Test Treatment A) and Tadalafil Chewable Tablets 20 mg *Fasted and With Water* (Test Treatment B), the mean score was 0.00.

Mucosal irritation assessments were also conducted by a physician and utilized a 4-point (0-3) scale, where 0 = None (normal), 1 = Mild (mild erythema plus slight edema), 2 = Moderate (moderate erythema and/or edema, e.g., beginning of tissue breakdown or sloughing; and 3 = Severe (severe inflammation/ irritation, e.g., definite blistering, ulceration, or epithelial sloughing. There was no evidence of mucosal irritation in any subject receiving either Tadalafil Chewable Tablets 20 mg *Fasted and Without Water* (Treatment A) or Tadalafil Chewable Tablets 20 mg *Fasted and With Water* (Test Treatment B). The mean score was 0.00.

> *Reviewer's Comment: Based upon the oro-mucosal irritation data and lack of oro-mucosal adverse event reports submitted in this NDA, it appears that Tadalafil Chewable Tablets do not cause oro-mucosal irritation.*

8.6. Safety Analyses by Demographic Subgroups

Not Applicable.

8.7. Specific Safety Studies/Clinical Trials

There were no specific safety studies conducted for this 505(b)(2) NDA.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

Not Applicable. This is a 505(b)(2) application. See reference product labeling.

8.8.2. Human Reproduction and Pregnancy

Not Applicable. This is a 505(b)(2) application. See reference product labeling.

8.8.3. Pediatrics and Assessment of Effects on Growth

Not Applicable. Erectile dysfunction is a condition of adult men. A waiver of required pediatric studies was granted.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Not Applicable. This is a 505(b)(2) application. See reference product labeling.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

As part of their Integrated Summary of Safety (ISS), the Sponsor conducted a robust review of the tadalafil postmarketing experience, which included searches of the published medical literature and the U.S. FAERS dashboard. The Sponsor's postmarketing safety review covered the period from 2018 to 2023 (2018 is the year of the most recent USPI label update). According to the Sponsor, the results of their searches were consistent with the safety information already shown in the approved CIALIS USPI, with one exception, the approved label makes no mention of malignant melanoma. According to the Sponsor, the FAERS dashboard (Table 7) shows the following results:

PT Malignant Melanoma:		438
PT Malignant Melanoma in situ:		158
PT Metastatic Melanoma:		62
PT Malignant Melanoma	Stage 1	60
	Stage 2	55
	Stage 3	42
	Stage 4	53
Lentigo Maligna		32
Nodular Melanoma		6

According to the Sponsor, the FAERS dashboard (Table 8) shows the following deaths reported with the diagnoses of:

Metastatic Malignant melanoma	29
Malignant melanoma	27
Malignant melanoma stg IV	16
Malignant melanoma stg II	12
Malignant melanoma stg III	8
Malignant melanoma in situ	7
CNS melanoma	1
Lentigno maligna	1
Malignant melanoma stage	1
Superficial Spreading Melanoma state unspecified	1

Reviewer's Comment: From 2014 to 2017, the FDA conducted an extensive review of PDE5i and melanoma under a Tracked Safety Issue/Newly Identified Safety Signal (TSI/NISS). At the time, we concluded that a causal relationship between melanoma and PDE5i could not be established. The Sponsor's review covers the period after the FDA's TSI/NISS review. (b) (4) *Our opinion remains the same as in 2017, a causal relationship between melanoma and PDE5i has not be established.*

8.9.2. Expectations on Safety in the Postmarket Setting

The clinical review team does not expect a change in the safety profile for use of this product in the adult population compared to the reference product Cialis and did not identify any new safety signals or trends requiring postmarketing analyses. Refer to the reference product labeling for the current postmarketing safety profile.

One potential safety issue identified was that this new chewable product contains a bubble gum flavoring which could make the product attractive to children. The Sponsor is aware of this potential risk and has packaged their product in bottles with child-resistant closure caps. They have also included in product labeling the instruction to "keep out of reach of children." This packaging was determined to be acceptable by the OPQ and DMEPA review teams.

8.9.3. Additional Safety Issues From Other Disciplines

There are no additional safety issues from other disciplines.

8.10. Integrated Assessment of Safety

The Sponsor has adequately established a scientific bridge to the listed drug, Cialis, based on data generated in their comparative bioavailability studies TADA-22-008, TADA-22- 051 and TADA-23-023 that demonstrated bioequivalence of Tadalafil Chewable Tablets 20 mg to Cialis Tablets 20 in male volunteers, in both fasted state and fed states. There was a modest prolongation of Tmax in the fed state that was reviewed by the Clinical Pharmacology review team and was concluded not to adversely affect efficacy or safety as compared to the approved product. The Sponsor also demonstrated bioequivalence in male volunteers taking Tadalafil Chewable Tablets with and without water. Based on the successful establishment of bioequivalence, all safety information shown in approved Cialis labeling is applicable to Tadalafil Chewable Tablets and may be relied upon in support of product safety and class labeling.

The Sponsor also submitted safety data they collected in a total of 94 subjects who received at least one dose of the new product in 4, Phase 1, comparative bioavailability studies, including the 3 studies mentioned above, and the Sponsor's first study, TADA-21-079, that used a different formulation. The Sponsor also submitted oro-mucosal irritation assessment data to support the safety of their product when chewed. This clinical data was determined to be acceptable.

Finally, the Sponsor submitted a robust review of the postmarketing safety experience for the listed drug, Cialis. No new safety signals or trends in the safety profile for Cialis was identified by the Applicant or the clinical review team.

In summary, in the completed BE studies that support this NDA submission:

- Two clinical adverse events (one each: vomiting and pyrexia) were reported in a total of 2 subjects. These 2 clinical events do not affect the safety profile reflected in the approved Cialis labeling.
- Sixteen abnormal laboratory findings were reported in 14 subjects. Of these, 8 were reports of abnormal liver function tests in 6 subjects, 4 were reports of decreased

hemoglobin in 4 subjects, 2 were reports of glucose increased in 2 subjects, and 2 were reports of eosinophil number increased in 2 subjects. The cases of abnormal labs were reviewed in detail and in summary, the evidence does not suggest causal relationship of the lab adverse events to study drugs. Instead, it appears that laboratory abnormalities at baseline, lab results variability, study design issues (e.g., outpatient setting, time between dosing) and intercurrent factors, and other unknown factors, may have played a role in the lab adverse events.

- Mucosal irritation data from studies TADA-22-051 and TADA-23-023 do not indicate a potential for clinically significant oro-mucosal irritation with Tadalafil Chewable Tablets.
- The Sponsor's review of published literature regarding postmarketing safety information for tadalafil (using MEDLINE via PubMed) did not indicate a need for a change from the safety information reflected in the USPI for Cialis Tablets.
- The Sponsor's review of 1214 individual adverse event reports that met the search eligibility criteria associated with tadalafil use in FDA's Adverse Event Reporting System (FAERS) over the period January 1, 2018, to June 1, 2023 also did not indicate a need for change in the safety information reflected in the USPI for Cialis Tablets.

Overall, there were no clinical findings, new safety signals or safety trends that alter the benefit/risk considerations of the reference product, Cialis Tablets

Advisory Committee Meeting and Other External Consultations

There was no advisory committee meeting nor external consultations necessary for this new formulation NDA.

9. Labeling Recommendations

9.1. Prescription Drug Labeling

On February 21, 2024, the FDA received proposed labeling from Sponsor. This was reviewed by FDA in multiple multidisciplinary meetings.

From the Clinical perspective, major modifications to Sponsor's proposed labeling were few:

9.2. Nonprescription Drug Labeling

Not Applicable.

10. Risk Evaluation and Mitigation Strategies (REMS)

There are no risk evaluation and mitigation strategies (REMS) necessary to support approval of this 505(b)2 NDA.

11. Postmarketing Requirements and Commitments

No PMR or PMCs are necessary to provide further support for this 505(b)2 NDA.

12. Appendices

12.1. References

Not Applicable.

12.2. Financial Disclosure

In Module 1.3.4 of this NDA submission, the Sponsor included FDA Form 3454/Certification: Financial Interests and Arrangements of Clinical Investigators for the following studies:

- TADA-21-079 (initial formulation): Three principal investigators total and identified
- TADA-22-008 (final formulation): Two principal investigators total and identified
- TADA-22-051 (final formulation): Three principal investigators total and identified
- TADA-23-023 (final formulation): Three principal investigators total and identified

The Clinical review team assessed the information in Module 1.3.4. No investigator had a financial disclosure. FDA Form 3455 was provided.

Covered Clinical Study (Name and/or Number):

Was a list of clinical investigators provided:	Yes x☐	No ☐ (Request list from Applicant)
Total number of investigators identified: 11 investigators total for all 4 studies. All participated in more than one study.		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) N/A
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) N/A
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 2		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) N/A

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/s/

A R WIEDERHORN
05/30/2024 12:53:25 PM

MARK S HIRSCH
05/30/2024 03:56:08 PM
As Clinical TL and CDTL, I concur.

AUDREY L GASSMAN
05/30/2024 03:57:16 PM
I concur with the approval recommendations of the clinical review team