CLINICAL REVIEW

Application Type	NDA Supplement
Application Number(s)	021368/S-030
Priority or Standard	Standard
Submit Date(s)	August 21, 2017
Filing Date(s)	October 20, 2017
PDUFA Goal Date	February 21, 2018
Division/Office	Division of Neurology Products
Reviewer Name(s)	Rainer W. Paine, MD, PhD
Review Completion Date	January 23, 2018
Established/Proper Name	tadalafil
Trade Name	Cialis®
Applicant	Eli Lilly and Company
Dosage Form(s)	tadalafil (Cialis) tablet strengths (2.5-, 5-, 10-, and 20-mg)
Purpose of the Application	To fulfill the terms of the Written Request – Amendment #3 issued by the FDA on August 3, 2017
Recommendation on Regulatory Action	No change to indications. The clinical terms of the Written request have been met.

Table of Contents

Table of Tables

Table of Figures

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
DMD	Duchenne muscular dystrophy
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
LOCF	last-observation-carried-forward
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
NSAA	North Star Ambulatory Assessment
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PAH	Pulmonary arterial hypertension
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
WR	written request
6MWD	6-minute walk distance

1. Executive Summary

1.1. Product Introduction

Tadalafil (Cialis®) is an orally administered, selective, reversible inhibitor of the enzyme phosphodiesterase type 5 (PDE5), the primary cyclic guanosine monophosphate (cGMP) hydrolyzing enzyme in smooth muscle. It has received FDA approval for the following indications: treatment of erectile dysfunction (NDA 021368, November 21, 2003); treatment of benign prostatic hyperplasia (NDA 021368/S020, October 6, 2011).; and the treatment of pulmonary arterial hypertension (NDA 022332, May 22, 2009, trade name Adcirca®).

Clinical development of tadalafil for the treatment of pediatric Duchenne muscular dystrophy (DMD) was conducted under IND 116994, which was submitted to FDA on April 19, 2013. The applicant studied tadalafil for the treatment of seven to fourteen-year-old males with DMD in a randomized, double-blind, placebo-controlled, Phase 3 trial (study H6D-MC-LVJJ, or "study LVJJ") under a Written Request (WR). Study LVJJ did not meet its primary or secondary endpoints. The applicant is therefore proposing to update the "Pediatric Use Subsection" of labeling with information about the negative study and is not proposing a new indication to the existing Cialis label.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Study LVJJ failed to meet its primary or secondary endpoints. There is no evidence from this study to support the efficacy of tadalafil in the treatment of patients with DMD.

2. Therapeutic Context

2.1. Analysis of Condition

Duchenne muscular dystrophy (DMD) is a progressive, X-linked recessive muscle disorder due to mutations in the DMD (dystrophin) gene that leads to loss of ambulation, cardiac and respiratory failure, and death typically by age 30 despite treatment. The disease affects approximately 1 in 3600-6000 male births and has a prevalence of approximately 1 in every 7,250 males aged 5 – 24 years (Romitti et al., 2015). It is the most common and most severe form of muscular dystrophy.

Female manifesting carriers are rare. Between 2.5 and 17% of carriers can show mild muscle weakness or even a DMD-like muscular dystrophy. Carriers are also at increased risk of cardiomyopathy.

Affected children present with symptoms such as abnormal gait and proximal weakness between the ages of 3 and 5 years. They often have difficulty climbing stairs, hopping, or arising from the floor, as well as cognitive impairment. Some signs of the disease may be present in infancy, although most parents only become aware of them retrospectively.

The clinical course is characterized by a developmental improvement in strength until about age 6 or 7, a plateau phase lasting up to 18 months, followed by progressive decline. Without treatment, ambulation is usually lost by age 12. Following the loss of ambulation, there is progressive loss of arm movements, increasing respiratory insufficiency and scoliosis, and cardiomyopathy. Without treatment, death usually occurs by age 20 years due to respiratory failure and cardiomyopathy.

Diagnosis can be made through a combination of family history, clinical features, laboratory markers (elevated serum creatine kinase (CK)), muscle histopathology, and genetic analysis. Newborn screening is available based on elevated CK levels and DNA mutational analysis (Hilton-Jones & Turner, 2014).

2.2. Analysis of Current Treatment Options

Treatment for DMD has generally been limited to corticosteroids and supportive care.

The American Academy of Neurology (AAN) practice guideline (Gloss et al., 2016) for corticosteroid treatment of Duchenne muscular dystrophy recommends prednisone and deflazacort as therapy for DMD. There are varying degrees of reported evidence that

prednisone may improve strength, pulmonary function, timed motor function, may reduce the need for scoliosis surgery, and delay cardiomyopathy onset. Published studies suggest that deflazacort may improve strength and timed motor function, delay the age at loss of ambulation by up to 3 years or more, improve pulmonary function, reduce the need for scoliosis surgery, delay cardiomyopathy onset, and increase survival at 5–15 years of follow-up.

Corticosteroids have numerous adverse effects, such as Cushing syndrome and adrenal crisis upon acute withdrawal, that limit their long-term use and tolerability. Published studies suggest that prednisone may be associated with greater weight gain in the first years of treatment than deflazacort. Deflazacort may be associated with a greater risk of cataracts than prednisone. Prednisone is associated with significant risk of weight gain, hirsutism, and Cushingoid appearance (Gloss et al., 2016).

Supportive care may include physical therapy, orthopedic appliances such as braces and wheelchairs, as well as appropriate cardiac, respiratory, nutritional, and mental health support. The first FDA-approved treatment for DMD, eteplirsen, was approved in 2016. Eteplirsen was approved using the accelerated approval pathway based on a small increase in dystrophin production in patients with DMD caused by mutations that are amendable to exon 51 skipping. Clinical efficacy of eteplirsen has not been established. Deflazacort was approved for the treatment of DMD patients 5 years of age and older on February 9, 2017.

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

The applicant submitted a Proposed Pediatric Study Request (PPSR) to study tadalafil in pediatric subjects with pulmonary arterial hypertension (PAH) in November 2005. The FDA in response then issued a Written Request to study tadalafil in pediatric subjects with PAH (IND 71871) on November 16, 2006. The WR was amended on April 12, 2010 to extend the timeframe for reporting from October 1, 2009, to August 20, 2017.

The applicant states that it was approached in September 2012 by clinical research and patient advocacy representatives from the DMD community with an unsolicited request to collaborate on a registration study of tadalafil in boys with DMD. Based on tadalafil's mechanism of action and nonclinical data, it was hypothesized that tadalafil might restore normal skeletal muscle hemodynamic responses to exercise and ameliorate progressive muscle damage in DMD. Although there were only exploratory clinical data from two small single-dose pilot studies to support this hypothesis, it was anticipated that tadalafil might be used in practice on patients with DMD.

In response to a subsequent PPSR, the Agency therefore agreed to amend the WR on September 17, 2015, to include a Phase 3 clinical study in pediatric subjects with DMD (IND 116994), pharmacokinetic analyses, and a juvenile rat toxicology study. The applicant subsequently notified FDA of its reported inability to complete the PAH study component of the WR due to inadequate enrollment, and requested that the PAH study be removed from the WR so that pediatric exclusivity might be granted solely based on the DMD study. This request was initially denied by FDA due to the need for information on the efficacy and safety of tadalafil in pediatric PAH patients. Following a cycle of appeals, the request was ultimately granted because the Agency deciding authority concluded that "factors currently exist that preclude the successful design and completion of the needed study or studies in PAH" (July 26, 2017, Appeal Granted letter). A third amendment to the Written Request was issued by FDA on August 4, 2017, removing the sections relating to PAH.

On March 17, 2015, the applicant submitted a request to the FDA Office of Orphan Products Development for orphan-drug designation for tadalafil for the treatment of DMD. On May 4, 2015, the applicant received an orphan-drug designation for the DMD indication (Designation Request #15-4764). Pediatric Exclusivity was granted for studies conducted on tadalafil on November 16, 2017.

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

4.1. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer reports that the applicant's submission contains dose range-finding and definitive studies of tadalafil in juvenile rats conducted in support of the Written Request. "The No-Observed-Adverse-Effect-Level (NOAEL) in both the non-GLP 2-week dose range-finding study and the definitive GLP 11-week study in juvenile rats administered tadalafil via oral gavage was the high dose of 1000 mg/kg/day. The definitive study was appropriately conducted. The study submitted adequately assesses the safety of oral tadalafil in juvenile rats. Therefore, the nonclinical terms of the Written request have been fairly met."

4.2. Clinical Pharmacology

The Office of Clinical Pharmacology (OCP) reviewed the Written Request and concluded that the applicant has fulfilled items in the WR that are relevant to the clinical pharmacology discipline. The relevant WR items along with the responses from the Applicant and OCP are discussed in the separate clinical pharmacology review.

5. Review Strategy

5.1. Sources of Clinical Data

This submission contains the results of the applicant's study H6D-MC-LVJJ ("Study LVJJ"), which was conducted under a Written Request (WR). Study LVJJ did not meet its primary or secondary efficacy endpoints, so no change in the existing indications for tadalafil is warranted. Safety data from study LVJJ are reviewed to ensure that they are consistent with the known safety profile of tadalafil.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study H6D-MC-LVJJ

The following study description is copied from the submission.

6.1.1 Title

A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial of Tadalafil for Duchenne Muscular Dystrophy

6.1.2 Objective

Primary Objective:

To test the hypothesis that once-daily tadalafil administered orally for 48 weeks lessened the decline in ambulatory ability as measured by the 6-minute walk distance (6MWD) compared to placebo in subjects with Duchenne muscular dystrophy (DMD).

Secondary Objectives:

- To test the hypothesis that once-daily tadalafil administered orally for 48 weeks compared with placebo in subjects with DMD:
    - lessened the decline in North Star Ambulatory Assessment (NSAA) global score;
    - lessened the decline in performance on timed function tests: rise from floor from supine, 10 meter walk/run, stair climb, and stair descend;
    - delayed the time to persistent 10% worsening in the 6MWD;

- delayed the time to persistent 10% worsening in timed function tests: rise from floor from supine, 10 meter walk/run test, stair climb, and stair descend;
- and lessened the decline in quality of life (QoL), as measured by the Pediatric Outcomes Data Collection Instrument (PODCI) global functioning scale and the following core scales: Upper Extremity/Physical Functioning, Transfer/Basic Mobility, and Sports/Physical Functioning (Daltroy et al. 1998)

- To characterize the pharmacokinetics (PK) of tadalafil in pediatric DMD subjects, and assess relationships between tadalafil exposure and efficacy and safety outcomes.

Exploratory objectives

- To assess whether once-daily tadalafil administered orally for 48 weeks compared with placebo in subjects with DMD:
  - lessened the decline in ambulatory ability as measured by: percent change from baseline in the 6MWD, and change from baseline in the percent of predicted 6MWD based on subject age and height as detailed in Geiger (2007)
  - lessened the decline in ambulatory ability as measured by individual components of the NSAA
  - lessened the decline in upper limb performance as measured by the Performance of the Upper Limb (PUL) scale
  - lessened the decline in pulmonary function as measured by spirometry
  - reduced resting heart rate as measured by electrocardiogram (ECG).

6.1.3 Design

Study LVJJ was a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel, 3-arm study of tadalafil 0.3 mg/kg and 0.6 mg/kg daily in subjects with DMD who were being treated with corticosteroids. The study consisted of a 48-week double-blind treatment period, followed by an open-label extension (OLE) phase.

6.1.4 Location

This study was conducted at 63 study centers in 15 countries.

6.1.5 Duration

The study consisted of a 48-week double-blind treatment period, followed by an open-label extension (OLE) phase. After the applicant's review of topline results from the double-blind period, the applicant made the decision that the study should be stopped, as the primary and key secondary endpoints were not met.

- Date of first subject enrolled: 16 September 2013
- Date of last subject visit in the double-blind treatment period: 16 December 2015

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6.1.6 Sample Size/Number of Subjects

- Planned: 102 tadalafil 0.3 mg/kg, 102 tadalafil 0.6 mg/kg, 102 placebo
- Randomized: 102 tadalafil 0.3 mg/kg, 113 tadalafil 0.6 mg/kg, 116 placebo
- Treated (at least 1 dose): 102 tadalafil 0.3 mg/kg, 112 tadalafil 0.6 mg/kg, 116 placebo
- Completed: 98 tadalafil 0.3 mg/kg, 107 tadalafil 0.6 mg/kg, 111 placebo

6.1.7 Key Inclusion Criteria

The following are among the key inclusion criteria for the trial:

- Males with DMD
- Age 7-14 years inclusive
- Ambulant, defined as 6MWD between 200 and 400 meters inclusive at screening and
- baseline
- Baseline 6MWD measurements within 20% of the screening 6MWD
- Left ventricular ejection fraction (LVEF) ≥50%
- Received systemic corticosteroids for a minimum of 6 months immediately prior to screening

6.1.8 Key Exclusion Criteria

The following are among the key exclusion criteria for the trial:

- Symptomatic cardiomyopathy, heart failure, or cardiac rhythm disorder
- Use of continuous mechanical ventilator assistance
- Use of any pharmacologic treatment, other than corticosteroids, that might have had an effect on muscle strength within 3 months prior to the start of study treatment
- Conditions which may have affected performance on functional outcome measures

6.1.9 Concomitant Medications

The protocol outlines the following restrictions with respect to the use of concomitant medications during the trial:

- Subjects receiving corticosteroid therapy that was initiated at a dose or regimen not generally recognized in care guidelines, practice parameters, or the published literature to be effective in the treatment of DMD were not to be eligible to enroll in the study.
- If the need for concomitant medication arose, inclusion or continuation of the subject was at the discretion of the investigator after consultation with the applicant.

6.1.10 Dosage

Tadalafil was administered orally once daily at one of 2 target doses (0.3 mg/kg or 0.6 mg/kg). A dosing algorithm was used to achieve each of the 2 daily target doses in different weight categories using a combination of existing tadalafil (Cialis) tablet strengths (2.5-, 5-, 10-, and 20-mg) or matching placebo tablets. Total daily dose during the double-blind treatment period was determined by the subject's weight at Visit 1 and was not adjusted based on changes in weight during the 48-week period. Placebo tablets were given orally to the control group once daily.

6.1.11 Schedule

The following table, copied from the submission, outlines the schedule of study procedures.

Table 1: **Schedule of Study Procedures for Study LVJJ.**

Study Schedule (Double-Blind Treatment Period)

	Screening	Baseline	Double-Blind Treatment Period					
Visit[a]	1	2	3	4	5	6	7	ET
Weeks		W0	W4	W12	W24	W36	W48	
Days	Day -20 to -1	Day 1	Day 29	Day 85	Day 169	Day 253	Day 337	
Visit Interval		± 10 days	± 3 days	± 5 days	± 5 days	± 5 days	± 5 days	± 5 days
Informed consent	X							
Medical history and preexisting conditions	X							
Complete physical exam	X							
Interval physical exam[b]			X		X		X	
Eye Exam[c]	X						X	X
Vital signs	X	X	X	X	X	X	X	X
Height and weight[d]	X		X	X	X	X	X	X
6-minute walk test (6MWT)[e]	X	X		X	X	X	X	X
North Star Ambulation Assessment (included rise from floor from supine and 10 meter walk/run tests)	X	X		X	X	X	X	X
Stair climbing/stair descending tests	X	X		X	X	X	X	X
Performance of the Upper Limb Scale	X	X		X	X	X	X	X
Pulmonary Function Tests		X					X	X
Blood Chemistry	X		X	X		X	X	X
Blood Hematology	X		X	X		X	X	X
Cystatin c	X		X				X	X
Urinalysis	X		X				X	X
PK sampling[f]			X	X	X	X		X
DNA stored sampling			X					
Biomarker Stored Samples	X		X		X			X[g]
12-lead ECG[h]	X				X		X	X
Echocardiogram (2D + M-mode)	X				X	X[i]	X	X[j]
PODCI Questionnaire		X		X	X		X	X
Adverse events	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X

	Screening	Baseline	Double-Blind Treatment Period					
Visit[a]	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**ET**
Weeks		**W0**	**W4**	**W12**	**W24**	**W36**	**W48**	
Dispense study drug[k]		X		X	X	X	X	
Drug return and accounting			X	X	X	X	X	X
Dystrophin Genetic Mutation[l]	X							

Abbreviations: 2D = 2-dimensional; 6MWD = 6-minute walk distance; 6MWT = 6-minute walk test; DMD = Duchenne muscular dystrophy; DNA = deoxyribonucleic acid; ECG = electrocardiogram; ET = early termination; LVEF = left ventricular ejection fraction; PK = pharmacokinetic; PODCI = Pediatric Outcomes Data Collection Instrument; W = week.

[a] For all office visits when functional assessments were performed, patients were to be advised to avoid strenuous or excessive physical activity beyond their normal activities for 48 hours prior to their visit.

[b] Focused physical examination with regard to any change in medical condition or known comorbidities of the patient since the last visit.

[c] Eye examination included patient medical eye history, external eye examination, and retinal examination using ophthalmoscopy.

[d] Height and weight were to be measured according to standardized procedure to the extent possible based on a patient's physical condition and state of disease progression at the time of the assessment. Supine stadiometer could be used, if needed.

[e] 6MWD at Visit 2 had to be within 20% of the screening 6MWD to be eligible for randomization.

[f] Sampling at these visits was to be scheduled within the following intervals: 1-3 hours postdose (4 weeks), 6-9 hours postdose (12 weeks), 12-18 hours postdose (24 weeks), and 24 (±1) hours postdose but prior to the subsequent dose (36 weeks). At Visits 5 and 6, patients were instructed not to take study drug on the visit day until after the PK sample had been collected but prior to administration of the 6MWT. The patient's weight was obtained and recorded at each PK sampling visit.

[g] Sample was taken only if ET occurred prior to Visit 5.

[h] ECGs were performed and reviewed at the study clinic and were sent to a vendor to be centrally read. Patients had to be supine for approximately 5-10 minutes before ECG collection and remain supine, but awake, during ECG collection.

[i] Echocardiogram was performed at 36 weeks only if a patient had a documented 10% or more absolute decline in LVEF at 24 weeks.

[j] If a patient terminated the study prior to Visit 5, an echocardiogram was not required.

[k] There were cases where actual dispensing of study drug was via courier once laboratory results/echocardiogram had been returned and evaluated.

[l] Dystrophin Gene Mutation was only performed on patients who did not have a documented genetic assessment that determined DMD diagnosis, and was not required if the patient met DMD diagnostic criteria by clinical history and record of muscle biopsy showing near-complete absence of dystrophin expression. This test was done locally by a certified lab.

6.1.12 Outcome Measure

Primary endpoint:

- 6-minute walk distance (6MWD)

Secondary endpoints:

- North Star Ambulatory Assessment (NSAA)
- Timed function tests (rise from floor from supine, 10 meter walk/run, 4-stair climb/descend)

Exploratory endpoints:

- Performance of the Upper Limb (PUL) Scale
- Pulmonary function tests
  - Forced vital capacity (FVC)
  - Peak expiratory flow (PEF)
  - Forced expiratory volume at 1 second (FEV1)
  - Calculated FEV1/FVC ratio
- Heart rate at rest
- Brachial Artery Ultrasound and Near-Infrared Spectroscopy after exercise
- Lower Limb Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS)
- Cardiac MRI

Quality of life: The American Academy of Orthopaedic Surgeons Pediatric Musculoskeletal Function Instrument [Pediatric Outcomes Data Collection Instrument (PODCI); parent-rated and adolescent self-reported]

Safety: Adverse events (AEs), vital signs (including height and weight), laboratory parameters, ECG, echocardiogram, eye examination

Pharmacokinetic/pharmacodynamic: Tadalafil PK was characterized with population pharmacokinetics methods using a one-compartment model established in adults.

6.1.13 Statistical Evaluation Methods

Efficacy

The applicant determined through sample size calculations that 306 subjects (102 per treatment arm) would be sufficient to detect a treatment difference of 30 meters with 90% power. Efficacy analyses were conducted on the full analysis set (FAS) on an intention-to-treat (ITT) basis. A mixed-effects model with repeated measures (MMRM) was used to test the primary null hypotheses of no difference between each treatment (tadalafil 0.3 mg/kg and 0.6 mg/kg) and placebo in mean change in 6MWD measured at 48 weeks.

Overall Type I error rate control was maintained for the primary comparisons using Hochberg's procedure (Hochberg 1988) whereas both null hypotheses were rejected if the maximum p-value was <.05. Sensitivity analyses including a joint rank analysis were also performed. Confirmatory testing of 5 secondary objectives was to occur if both null hypotheses (no difference at either of the two doses tested) for the primary objective were rejected. Based on the primary result, none of the secondary objectives could be tested in a confirmatory manner.

Safety

All safety analyses were conducted using only subjects that received at least one dose of study medication according to the treatment the subject actually received (safety analysis set). Change from baseline to endpoint treatment differences in vital signs, continuous laboratory parameters, and continuous ECG parameters were assessed pairwise using Wilcoxon rank-sum tests. Categorical safety measures were analyzed using Fisher's exact test. Adverse event summaries by AUC quartile were also analyzed using Fisher's exact test. Change in echocardiogram parameters was analyzed through an ANCOVA model with treatment as a factor and baseline as a covariate.

Demographic Characteristics

As described by the applicant, a total of 331 subjects with DMD were randomized to receive

placebo (N=116), tadalafil 0.3 mg/kg (N=102), or tadalafil 0.6 mg/kg (N=113) for 48 weeks. The mean age of subjects was 9.6 years. The majority of subjects were White (79.2%); non-White subjects included Asian (15.4%), Black or African American (2.1%), or Multiple races (2.1%). Mean 6MWD at baseline was 329 meters (54% of the predicted value for age and height). As required for inclusion in the study, all subjects were taking a corticosteroid at baseline, either prednisone/prednisolone (53.8%) or deflazacort (45.9%). Mean duration of corticosteroid therapy was 40.6 months at baseline, and most subjects (71.9%) were taking a daily corticosteroid regimen.

The applicant reports the following assessments. The treatment groups were generally balanced with regard to most demographic characteristics, although subjects in the tadalafil 0.3 mg/kg group were slightly older (mean, 9.9 years) compared to placebo (mean, 9.4 years), and this group had a higher proportion of subjects >10 years of age (32.4%) compared to the placebo group (17.2%) and the tadalafil 0.6 mg/kg group (19.5%). There were also small treatment group imbalances in a number of baseline functional characteristics (6MWD and % predicted 6MWD, proportion of subjects with baseline 6MWD <300 meters, proportion of subjects that could not rise from the floor or climb stairs independently) and the type and frequency of corticosteroid use. Although individually most of these differences were small, collectively they trended toward better baseline ambulation and general health status in the placebo group compared to the tadalafil groups, particularly the tadalafil 0.3 mg/kg group. Mean compliance across all treatment groups exceeded 97% at each visit.

6.1.14 Efficacy Results

The applicant reports the following results, copied from the submission, for study LVJJ.

Efficacy Results
Primary endpoint: Change in 6MWD from Baseline to Week 48

Tadalafil did not show efficacy in slowing the decline in ambulation as measured by the primary 6MWD endpoint: the least squares (LS) mean change in 6MWD at 48 weeks was -51.0 meters in the placebo group, compared with -64.7 meters in the tadalafil 0.3 mg/kg group (p=.307) and -59.1 meters in the tadalafil 0.6 mg/kg group (p=.538). The results of sensitivity analyses on the 6MWD (excluding subjects who lost ambulation during the trial, excluding subjects who discontinued study medication but remained in the trial, and a joint rank analysis which accounted both for the longitudinal 6MWD measure and time to loss of ambulation) were consistent with the primary analysis.

The following table, copied from the submission, shows the results of the primary endpoint analysis.

Table 2: Change in 6MWD from Baseline to Week 48

6-Minute Walk Distance (Meters) – Repeated Measures Analysis
Double-Blind Treatment Period
Full Analysis Set

Treatment	Time Point	n	Mean	SD	Median	LS Mean Change [a]	SE	Treatment Difference (Tadalafil vs Placebo)[a] LS Mean	SE	95% CI	p-value [b]
Placebo (N=116)	Baseline	113	337.13	48.469	351.00						
	Week 12	111	331.08	68.694	336.00	-5.83	4.117				
	Week 24	107	317.03	91.339	338.00	-20.93	6.179				
	Week 36	109	302.77	97.812	325.00	-38.34	7.516				
	Week 48	104	288.90	119.413	318.50	-50.99	9.316				
Tadalafil 0.3mg/kg (N=102)	Baseline	101	323.48	53.892	342.00						
	Week 12	100	308.83	85.759	326.00	-11.35	4.334				
	Week 24	98	295.32	106.433	321.00	-27.95	6.491				
	Week 36	95	279.82	123.125	310.00	-42.93	7.948				
	Week 48	95	259.60	141.152	292.00	-64.71	9.809	-13.71	13.396	(-40.08, 12.65)	0.307
Tadalafil 0.6mg/kg (N=113)	Baseline	111	325.68	55.949	342.00						
	Week 12	108	309.73	74.069	333.50	-13.12	4.110				
	Week 24	108	295.76	97.815	327.50	-27.82	6.181				
	Week 36	104	278.93	110.011	306.50	-44.47	7.586				
	Week 48	102	265.82	126.315	302.50	-59.08	9.397	-8.09	13.114	(-33.90, 17.72)	0.538

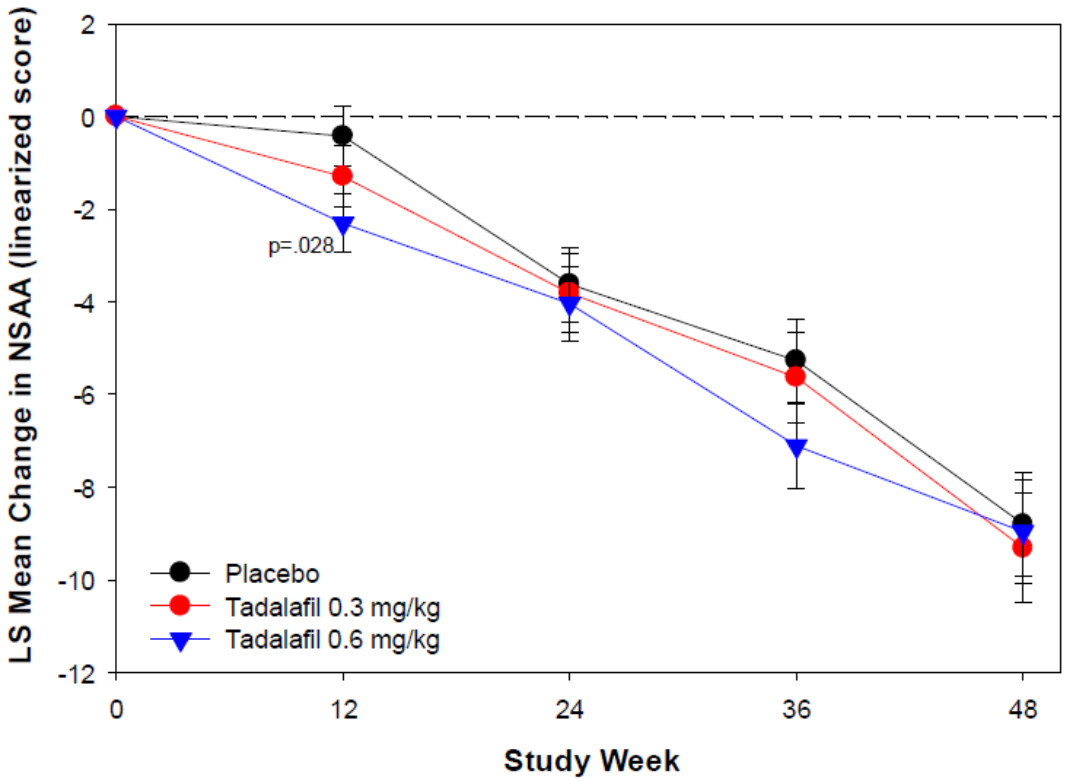
Abbreviations: 6MWD = 6-minute walk distance; CI = confidence interval; LS Mean = least-squares mean; n = number of patients at each visit with non-missing values; N = number of patients in the full analysis set; SD = standard deviation; SE = standard error.
Note: In cases where a patient completely loses ambulation, the patient's 6MWD is treated as zero for analysis purposes at all visits after ambulation was lost whether or not the 6MWD was formally attempted.
[a] The LS mean change from baseline, standard error, 2-sided 95% confidence interval and p-value are derived using mixed model repeated measures methodology with factors for pooled country, treatment, visit, treatment-by-visit interaction and baseline 6MWD as a covariate.
[b] Both null hypotheses with tadalafil compared to placebo will be rejected if the maximum p-value is <0.05. If at least one p-value is greater than 0.05, the corresponding null hypothesis for that p-value will not be rejected and the remaining hypothesis will be rejected if the corresponding p-value <0.025. Other p-values are provided for each factor/covariate in the model.

Secondary endpoints:

- North Star Ambulatory Assessment (NSAA)
  There was no evidence that tadalafil treatment slowed the decline in NSAA linearized score through 48 weeks. At 48 weeks, the LS mean change in linearized NSAA global score was -8.8 in the placebo group, -9.3 in the tadalafil 0.3 mg/kg group (p=.748), and -9.0 in the tadalafil 0.6 mg/kg group (p=.914).

  The following figure, copied from the submission, shows the least squares mean change from baseline in NSAA by study week.

Figure 1: LS mean change (±SE) from baseline in NSAA (linearized score) by study week



Abbreviations: LS = least squares; NSAA = North Star Ambulatory Assessment; SE = standard error.
Source: Table LVJJ.14.24.

- Timed function tests (rise from floor from supine, 10 meter walk/run, 4-stair climb/descend)
  Consistent with DMD disease progression, functional performance on all of the tasks declined over the 48 weeks as evidenced by increasing time required to complete each task, decreasing velocity, and a general reduction in functional grade. There were no overall treatment group differences in any of the analyses of timed function tests that suggested efficacy of tadalafil to slow the decline in these measures.

Exploratory endpoints:

- Performance of the Upper Limb (PUL) Scale
  There was no significant effect of tadalafil treatment on the PUL total score or any individual PUL domain score, with the exception of an increase (improvement) in the PUL distal-level hand domain at 48 weeks in the tadalafil 0.6 mg/kg group compared with placebo. The magnitude of this treatment difference was small (0.2 points on a 24-point scale) and not considered clinically meaningful. Time to perform each of the PUL timed tasks (lifting light or heavy cans, and stacking light or heavy cans) tended to

decrease in all treatment groups over the course of the study, with no significant treatment group differences at any time point.

- Pulmonary function tests
    - Changes in absolute and percent-predicted values for pulmonary function tests (forced vital capacity [FVC], forced expiratory volume at 1 second [FEV1], peak expiratory flow, and FEV1/FVC ratio) from baseline to endpoint also were small with no clinically meaningful treatment group differences.
- Heart rate at rest
    - There were no significant differences between either tadalafil treatment group and placebo in change from baseline in resting heart rate measured by ECG. In all treatment groups, decreases from baseline in resting heart rate were observed at Week 24 and Week 48. At Week 48, the LS mean decrease was -1.61 bpm in the placebo group, compared with -3.78 bpm in the tadalafil 0.3 mg/kg group (p=.182) and -2.35 bpm in the tadalafil 0.6 mg/kg (p=.635) groups.
- Brachial Artery Ultrasound and Near-Infrared Spectroscopy after exercise
    - Because of the small sample size (4 subjects at 48 weeks) and inherent variability in these measures, this addenda study did not provide sufficient data for meaningful clinical or statistical interpretation.
- Lower Limb Magnetic Resonance Imaging (MRI) and Magnetic Resonance Spectroscopy (MRS)
    - No significant treatment group differences were observed for change in any MRI or MRS parameter analyzed as either baseline to 24 week change, baseline to 48 week change, or baseline to LOCF endpoint change.
- Cardiac MRI
    - There were no significant treatment group differences in mean change from baseline to endpoint on circumferential wall strain or LVEF. Left ventricular (LV) end diastolic volume increased from baseline to endpoint in the tadalafil 0.3 mg/kg group (13.0 mL, p=.047) and the tadalafil 0.6 mg/kg group (12.0 mL; p=.080) compared with placebo (1.2 mL). Left ventricular end systolic volume also increased to a numerically greater extent in both the tadalafil 0.3 mg/kg group (5.8 mL, p=.074) and the tadalafil 0.6 mg/kg group (6.2 mL, p=.073) compared with placebo (0.1 mL). Mean changes in stroke volume, cardiac output, and LV mass from baseline to endpoint also increased to a numerically greater extent in the tadalafil groups compared with placebo. There were no significant treatment group differences in mean change from baseline to endpoint on measures of right ventricular function.

Quality of life: The American Academy of Orthopaedic Surgeons Pediatric Musculoskeletal Function Instrument [Pediatric Outcomes Data Collection Instrument (PODCI); parent-rated and adolescent self-reported]

Functional quality of life changes were measured using the PODCI global functioning scale and 3 core scales of interest from the PODCI questionnaire: upper extremity/physical functioning, transfer/basic mobility, and sports/physical functioning. There were no significant differences between either tadalafil group and placebo on the mean changes on the parent-rated PODCI global functioning scale or any of the 3 core scales of interest.

Safety: Adverse events (AEs), vital signs (including height and weight), laboratory parameters, ECG, echocardiogram, eye examination

Pharmacokinetic/pharmacodynamic: Tadalafil PK was characterized with population pharmacokinetics methods using a one-compartment model established in adults.

Clinical Reviewer Comment: The single Phase 3 study of tadalafil (Study LVJJ) in subjects with DMD failed to meet its primary or secondary endpoints. This study was well-conducted and included both treatment and placebo groups. It showed that there is no benefit in the treatment with tadalafil of patients with DMD.

6.1.15 Safety Results

The applicant reports that of the 331 randomized subjects, 330 received a dose of study medication. Mean adjusted exposure duration during the double-blind treatment period was similar across treatment groups (333 days placebo, 336 days tadalafil 0.3 mg/kg, and 330 days tadalafil 0.6 mg/kg). The subjects were also receiving corticosteroids throughout the study and 96.4% received ≥1 concomitant medication in addition to corticosteroids.

The most common (>=2%) adverse events in the tadalafil-treated group compared to placebo are shown in the following table, generated from a MAED analysis of the applicant's submitted data. These AEs are generally consistent with those listed in the current Cialis label listed below in Table 5. The AEs related to penile erection are consistent with the known effect of tadalafil. No events of priapism were reported.

Table 3: MAED analysis of submitted data showing adverse events in the tadalafil-treated group occurring in at least 2% of subjects compared to placebo. AEs that were more frequent in the tadalafil group are in bold print.

	Group ID 1: Tadalafil (N = 215)			Group ID 0: Placebo (N = 111)		
PT	Events	Number of subjects	Proportion (%)	Events	Number of subjects	Proportion (%)
Headache	126	77	**35.81**	86	34	**30.63**
Fall	91	47	21.86	49	30	27.03
Vomiting	42	31	**14.42**	19	14	**12.61**
Spontaneous penile erection	29	28	**13.02**	8	7	**6.31**
Erection increased	13	13	**6.05**	5	5	**4.5**
Back pain	16	13	6.05	12	7	6.31
Abdominal pain	12	12	**5.58**	8	6	**5.41**
Cough	16	12	5.58	11	10	9.01
Nausea	11	10	**4.65**	1	1	**0.9**
Epistaxis	15	9	**4.19**	3	1	**0.9**
Constipation	9	7	**3.26**	4	2	**1.8**
Gastroenteritis	7	7	3.26	4	4	3.6
Flushing	6	6	**2.79**	0	0	**0**
Fatigue	5	5	**2.33**	1	1	**0.9**
Myopia	5	5	**2.33**	1	1	**0.9**
Upper respiratory tract infection	5	5	2.33	5	3	2.7
Rhinitis	6	5	2.33	5	5	4.5
Dizziness	6	5	2.33	9	6	5.41

The following table shows the most common adverse events listed in the Cialis label approved for NDA supplement 29 in 2017.

Table 4: Most common adverse reactions listed in the current Cialis label

Treatment-Emergent Adverse Reactions Reported by ≥2% of Patients Treated with CIALIS (10 or 20 mg) and More Frequent on Drug than Placebo in the Eight Primary Placebo-Controlled Clinical Studies (Including a Study in Patients with Diabetes) for CIALIS for Use as Needed for ED

Adverse Reaction	Placebo (N=476)	Tadalafil 5 mg (N=151)	Tadalafil 10 mg (N=394)	Tadalafil 20 mg (N=635)
Headache	5%	11%	11%	15%
Dyspepsia	1%	4%	8%	10%
Back pain	3%	3%	5%	6%
Myalgia	1%	1%	4%	3%
Nasal congestion	1%	2%	3%	3%
Flushing[a]	1%	2%	3%	3%
Pain in limb	1%	1%	3%	3%

[a] The term flushing includes: facial flushing and flushing

The following table, copied from the applicant, lists the serious adverse events from the study. These SAEs appear to be consistent with the known complications of DMD and the corticosteroid treatment these subjects were receiving. No subjects died during Study LVJJ.

Table 5: Serious Adverse Events in Study LVJJ

Inv/ PatID/ Trt	System Organ Class/ Preferred Term/ Verbatim Term	Visit 1 Date/ Rand. Date	Start Date/ Stop Date/ Outcome	Serious Reason	Severity	Caused Disc.	TEAE	Rel. to Study Trt	Rel. to Study Proc	Rel. to Adjunct Trt
100-01011/ Tad 0.3	Musculoskeletal and connect ive tissue disorders/ Muscle contracture/ EQUINUS MUSCLE CONTRACTURES WORSENED CONDITION	2014-12-15/ 2014-12-16	2015-08-07/ / RR	HO	Severe	No	Yes	No	No	No
114-01703/ Pla	Infections and infestations / Bronchitis/ ACUTE BRONCHITIS	2014-04-07/ 2014-05-14	2015-04-11/ 2015-04-15/ R	HO	Severe	No	Yes	No	No	No
120-02001/ Tad 0.6	Injury, poisoning and proce dural complications/ Fall/ FALL	2014-04-09/ 2014-07-08	2015-01-27/ 2015-01-27/ R	HO	Severe	No	Yes	Yes	No	No
	Injury, poisoning and proce dural complications/ Femur fracture/ RIGHT FEMUR FRACTURE	2014-04-09/ 2014-07-08	2015-01-27/ 2015-01-30/ RS	HO	Severe	No	Yes	Yes	No	No
204-02705/ Pla	Injury, poisoning and proce dural complications/ Femoral neck fracture/ RIGHT FEMORAL NECK FRACTURE	2014-12-09/ 2014-12-11	2015-05-01/ / RR	HO	Severe	No	Yes	No	No	No
351-03552/ Pla	General disorders and admin istration site conditions/ Abasia/ LOSS OF AMBULATION	2014-01-23/ 2014-02-13	2014-06-01/ / NR	DA	Severe	No	Yes	No	No	No
400-04005/ Tad 0.3	Cardiac disorders/ Myocarditis/ MYOCARDITIS	2014-04-30/ 2014-05-09	2014-10-22/ 2014-10-31/ R	HO	Moderate	Yes	Yes	Yes	No	No
402-04101/ Tad 0.6	Musculoskeletal and connect ive tissue disorders/ Tendinous contracture/ CONTRACTURE RIGHT ACHILLES TENDON WORSENED	2013-11-27/ 2013-12-11	2014-05-21/ 2014-06-05/ RS	HO	Severe	No	Yes	Yes	No	No
402-04106/ Pla	Musculoskeletal and connect ive tissue disorders/ Tendinous contracture/ TENDINOUS CONTRACTURE	2014-02-19/ 2014-03-12	2014-07-15/ 2014-08-02/ RS	HO	Moderate	No	Yes	No	No	No
451-04560/ Pla	Injury, poisoning and proce dural complications/ Fall/ ACCIDENTAL FALL	2014-09-16/ 2014-10-13	2015-03-02/ 2015-03-02/ RS	HO,OTH	Moderate	No	Yes	No	No	No
	Injury, poisoning and proce dural complications/ Lower limb fracture/ BONE FRACTURE IN LEFT LEG	2014-09-16/ 2014-10-13	2015-03-03/ 2015-08-30/ RS	HO	Moderate	No	Yes	No	No	Yes
451-04561/ Tad 0.6	Injury, poisoning and proce dural complications/ Fall/ ACCIDENTAL FALL	2014-12-10/ 2015-01-09	2015-07-10/ 2015-07-10/ RS	HO	Moderate	No	Yes	No	No	No
	Injury, poisoning and proce dural complications/ Femur fracture/ FRACTURE IN LEFT FEMUR	2014-12-10/ 2015-01-09	2015-07-10/ / RR	HO	Moderate	No	Yes	No	No	Yes

454-04705/ Tad 0.3	Infections and infestations / Gastrointestinal infection/ GASTROINTESTINAL INFECTION	2014-09-23/ 2014-10-07	2015-05-23/ 2015-05-24/ R	HO	Severe	No	Yes	No	No	No
500-05004/ Tad 0.6	Infections and infestations / Pneumonia adenoviral/ ADENOVIRAL PNEUMONIA	2014-02-04/ 2014-02-18	2014-10-06/ 2014-10-10/ R	HO	Severe	No	Yes	No	No	No
600-06004/ Tad 0.6	Infections and infestations / Pharyngotonsillitis/ PHARINGOTONSILITIS	2013-11-21/ 2013-12-30	2014-04-28/ 2014-05-03/ R	HO	Mild	No	Yes	No	No	No
901-09051/ Tad 0.3	Infections and infestations / Pneumonia/ BRONCOPNEUMONIA	2014-07-14/ 2014-08-11	2015-02-26/ 2015-03-06/ R	HO	Moderate	No	Yes	No	No	No
901-09055/ Tad 0.6	Infections and infestations / Varicella/ VARICELLA INFECTION	2014-08-21/ 2014-08-28	2015-03-11/ 2015-03-19/ R	HO	Moderate	No	Yes	No	No	No

Abbreviations: Disc = discontinuation; Inv = investigator; PatID = patient identifier; Pla = placebo; Proc = procedure; Rand = randomization; Rel = related; Tad 0.3 = Tadalafil 0.3 mg/kg; Tad 0.6 = Tadalafil 0.6 mg/kg; TEAE = treatment-emergent adverse event; Trt = treatment.
Code: CA-Congenital Anomaly; D-Death; DIS-Disability; HO-Hospitalization; LT-Life threatening; OTH-Other Serious Criteria; NR-Not Recovered/Not Resolved; R-Recovered/Resolved; RR-Recovering/Resolving; RS-Recovered or Resolved with Sequelae; UNK-unknown.
Note: Ongoing events are designated by a missing event stop date.
Deaths are counted as Serious Adverse Events.
MedDRA Version 18.1

This reviewer concludes that the safety profile in Study LVJJ is consistent with that described in the current Cialis label and with the known complications of DMD treated with corticosteroids.

7 Labeling Recommendations

7.1 Prescription Drug Labeling

Based on the results of Study LVJJ, the following text is recommended for section 8.4 of the Cialis label.

> 8.4 Pediatric Use
> CIALIS is not indicated for use in pediatric patients. Safety and efficacy in patients below the age of 18 years have not been established.
>
> A randomized, double-blind, placebo-controlled trial in pediatric subjects (7 to 14 years of age) with Duchenne muscular dystrophy who received either 0.3 mg/kg, 0.6 mg/kg, or placebo daily for 48 weeks failed to demonstrate any benefit of treatment with CIALIS on a range of assessments of muscle strength and performance.

8 Appendices

8.1 References

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/s/

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02/09/2018

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