Office of Clinical Pharmacology Review

NDA	21368, S-030
Submission Date	8/21/17
Submission Type	Efficacy Supplement (Response to Pediatric Written Request)
Brand Name	Cialis™
Generic Name	Tadalafil
Dosage Form & Strength	Tablets
Route of Administration	Oral
Proposed Indication	None. Due to failed clinical program in boys with Duchenne Muscular Dystrophy (DMD)
Applicant	Eli Lilly and Company
OCP Review Team	Atul Bhattaram, Ph.D., Kevin Krudys, Ph.D., Sreedharan Sabarinath, Ph.D.

Background

Eli Lilly and Company conducted a clinical trial with tadalafil in boys with Duchenne Muscular Dystrophy (DMD) to fulfill the Written Request issued by the Agency. The Pediatric Written Request (PWR) for tadalafil was originally issued on 11/16/2006 and was subsequently amended (For more details, refer to the review by Dr. Rainer, Medical Officer, Division of Neurology Products, CDER).

Tadalafil is a selective, reversible inhibitor of cGMP-specific phosphodiesterase type 5 (PDE5). It was hypothesized that by inhibiting PDE5, the enzyme responsible for degrading cGMP (cyclic guanosine monophosphate), tadalafil may enhance the residual NO (nitric oxide) signaling coming from active skeletal muscle by selectively boosting cGMP bioavailability and inducing vasodilation as needed, in response to exercise.

The Applicant conducted a randomized, double-blind, placebo-controlled study (Study H6D-MC-LVJJ [LVJJ]) to evaluate the efficacy and safety of tadalafil 0.3 mg/kg and 0.6 mg/kg administered orally once daily in ambulatory boys with DMD who are receiving treatment with corticosteroids. A total of 331 boys 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 boys with DMD was 9.6 years. Mean 6-minute walk distance (6MWD) at baseline was 329 meters (54% of the predicted value for age and height). As required for inclusion in the study, all boys with DMD 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 (71.9%) were taking a daily corticosteroid regimen.

Dose selection was based on the single doses of tadalafil that were shown to restore normal hemodynamic responses in studies of adults with Becker's Muscular Dystrophy (BMD) and boys with DMD. In a randomized, placebo-controlled, crossover study in adult men (mean age, 37 years) with BMD, a single dose of 20 mg tadalafil alleviated microvascular ischemia and fully restored blood flow regulation (*Martin EA, Barresi R, Byrne BJ, Tsimerinov EI, Scott BL, Walker AE, Gurudevan SV, Anene F, Elashoff RM, Thomas GD, Victor RG. Tadalafil alleviates muscle ischemia in patients with Becker muscular dystrophy. Sci Transl Med. 2012;4(162):162ra155*). Based on an adult weight of 75 kg, this equates to a dose of approximately 0.3 mg/kg. In addition, single doses of tadalafil (0.5 mg/kg or 1.0 mg/kg) dose-dependently restored normal muscle hemodynamic responses to exercise in boys with DMD assessed by both functional sympatholysis (that is, the NO-dependent, exercise-induced attenuation of sympathetic vasoconstriction) and exercise-induced brachial artery hyperemia (*Nelson MD, Rader F, Tang X, Tavyev J, Nelson SF, Miceli MC, Elashoff RM, Sweeney HL, Victor RG. PDE5 inhibition alleviates functional muscle ischemia in boys with Duchenne*

muscular dystrophy. Neurology. 2014;82(23):2085-2091). Assuming a 1.6-fold accumulation factor during multiple dosing (*Forgue ST, Patterson BE, Bedding AW, Payne CD, Phillips DL, Wrishko RE, Mitchell MI. Tadalafil pharmacokinetics in healthy subjects. Br J Clin Pharmacol. 2006;61(3):280-288*), the exposures produced by a single dose of 0.5 mg/kg or 1.0 mg/kg equate to once-daily doses of approximately 0.3 mg/kg and 0.6 mg/kg, respectively. These once-daily doses are predicted to achieve steady-state exposures consistent with those that produced pharmacological effects on skeletal muscle hemodynamics in boys with DMD after a single dose.

In the study conducted by the Applicant as per the PWR, tadalafil did not show efficacy in slowing the decline in ambulation as measured by the primary 6MWD endpoint at 48 weeks. Refer to the review by Dr. Rainer, Medical Officer, Division of Neurology Products, CDER for more details.

Towards determining the pediatric exclusivity, the Office of Clinical Pharmacology (OCP) reviewed relevant aspects that were in the Written Request. The review team has concluded that the Applicant has fulfilled items in the PWR that are relevant to clinical pharmacology discipline. The relevant PWR items along with the responses from the Applicant and OCP are discussed below.

Written Request Item #1: Clinical Study

Tadalafil pharmacokinetics (PK) and relationships between tadalafil exposure and efficacy and safety will be characterized using a population PK (PPK) approach. Patients will be randomized to one of two doses of tadalafil or placebo in a 1:1:1 ratio.

Information Submitted/ Applicant's response

Tadalafil pharmacokinetics were characterized with population PK methods using a one-compartment model established in adults. Patients in Study LVJJ were randomized to either placebo treatment or 0.3 mg/kg or 0.6 mg/kg tadalafil dose.

OCP's Comments

Fulfilled as stated in PWR

The Applicant conducted population pharmacokinetic analyses using acceptable methodology that included base model development along with screening of covariates for their influence on tadalafil pharmacokinetics. The analysis report along with the data has been submitted to the Agency.

Written Request Item #2: Study Endpoints

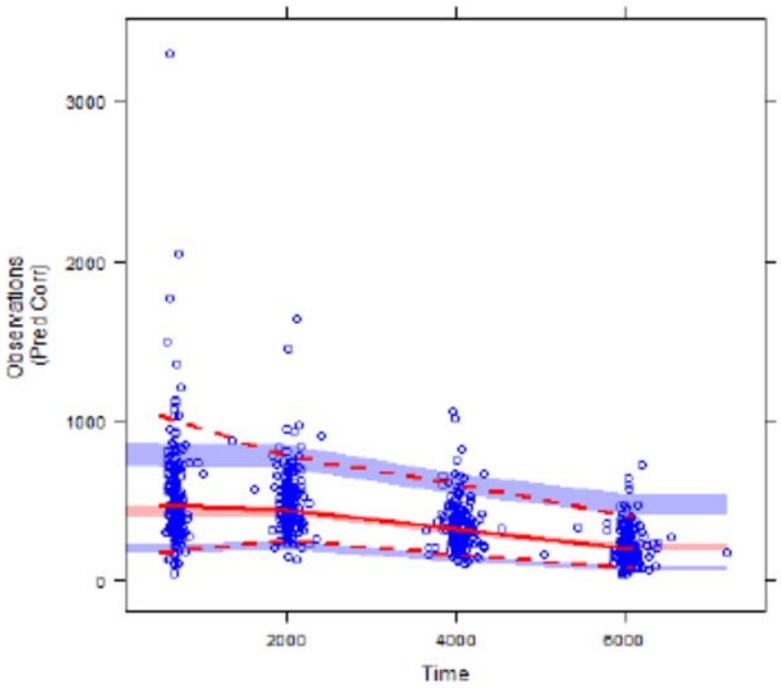
Pharmacokinetic/Pharmacodynamic Endpoints:

The pharmacokinetic endpoints in the population pharmacokinetic analysis must include volume of distribution and clearance. Sparse pharmacokinetic samples must be collected to explore the relationships between tadalafil exposure and efficacy and safety endpoints.

Information Submitted/ Applicant's response

Pop PK Report:

Covariate Selection and Final Model



Abbreviations: PK = pharmacokinetic; Pred Corr = prediction correction.
Blue circles represent observed data; Blue shaded regions represent 95% confidence interval around the 5th and 95th percentile tadalafil concentrations calculated from 500 simulation replicates across all doses with prediction correction; the red lines represent the median (solid red) and the 5th and 95th percentiles (dashed red) of the observed data; the red shaded region represents the 95% confidence interval of the median from the simulated data.
Units: Time is in hours and Observations are in ng/mL.

Source: Figure 6.3 on page 20 in population-pk-report.pdf

Estimates of apparent clearance and apparent volume of distribution in the final population PK model were 1.79 L/hr and 39.1 L, respectively.

Table 6.4. Pharmacokinetic and Covariate Parameters in Final Population Model

Parameter Description	Population Estimate (%SEE)	Inter-Patient Variability (%SEE)
Bioavailability		
Parameter for F	1 (fixed)	---
Effect of dose (continuous) on F[a]	-0.0191 (11.7)	---
Rate of Absorption		
Parameter for Ka (hr^{-1})	0.716 (16.1)	263% (22.8)
Clearance		
Parameter for CL/F (L/hr)	1.79 (2.28)	29.6% (13.1)
Volume of Distribution		
Parameter for V/F (L)	39.1 (4.07)	--- ---
Effect of body weight on V/F (kg^{-1})	1 (fixed)	
Residual Error		
Additive (ng/mL)	0 (fixed) [b]	
Proportional	25.7% (9.16) [c]	

Abbreviations: F = bioavailability; CL/F = apparent clearance; K_a = absorption rate constant; SEE = standard error of the estimate; V/F = apparent volume of distribution.

[a] The effect of dose on F is described by 1•exp(-0.0191• (dose-15)), where 15 is the median dose.

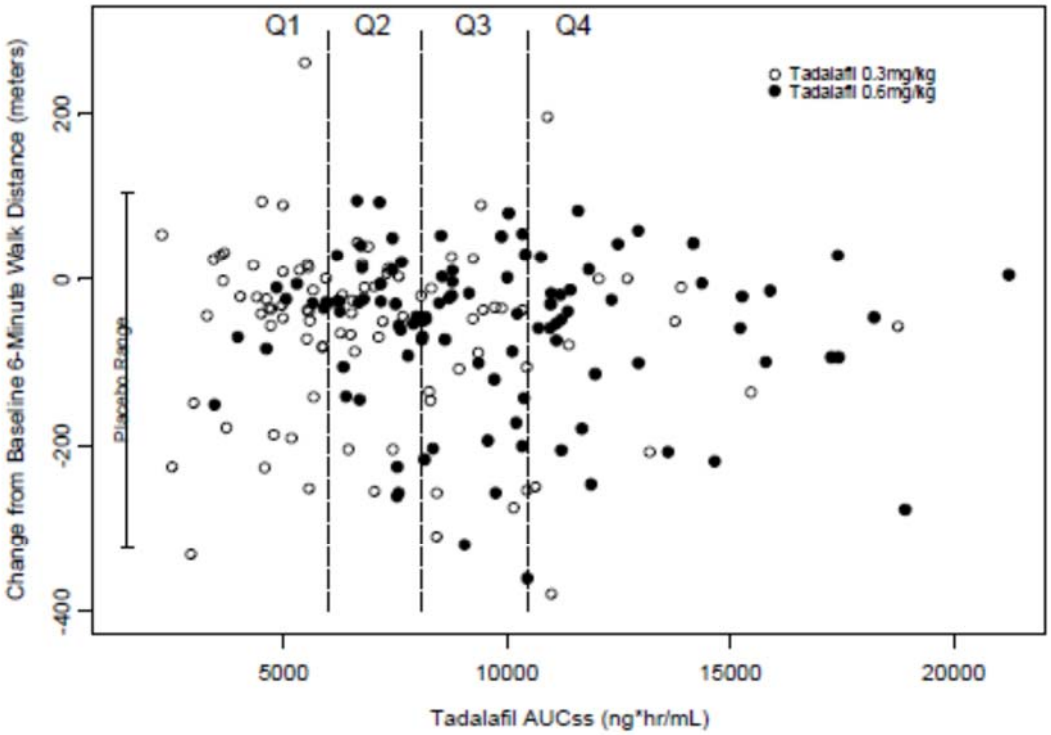
[b] During final modeling the ratio of additive proportional error was fixed to 0.

[c] The proportional residual error is calculated as SQRT(SIGMA(1)) • 100%.

Source: Table 6.4 on page 21 in population-pk-report.pdf

Pop PK Report:

Exposure-Efficacy Relationship: The relationship between the study's primary efficacy outcome and tadalafil exposure was evaluated from a scatterplot of change from baseline in 6-minute walk distance (6MWD) at Week 48 versus tadalafil AUC. There was no discernable relationship between AUC and change in 6MWD.



Abbreviations: AUCss = area under the curve of concentration versus time at steady state.

Source: Figure 6.6 on page 26 in population-pk-report.pdf

Results of statistical analyses of relationships between adverse events and AUC quartile are also provided.

Preferred Term	Exposure										p-value [a]
	1st AUC Quartile		2nd AUC Quartile		3rd AUC Quartile		4th AUC Quartile		Total		
	(N=52) n	(%)	(N=53) n	(%)	(N=52) n	(%)	(N=53) n	(%)	(N=210) n	(%)	
Conjunctival hyperaemia	1	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0.495
Conjunctivitis	1	(1.9)	0	(0.0)	1	(1.9)	1	(1.9)	3	(1.4)	0.808
Conjunctivitis allergic	2	(3.8)	0	(0.0)	1	(1.9)	0	(0.0)	3	(1.4)	0.150
Constipation	2	(3.8)	2	(3.8)	1	(1.9)	0	(0.0)	5	(2.4)	0.579
Contusion	1	(1.9)	1	(1.9)	0	(0.0)	3	(5.7)	5	(2.4)	0.404
Cough	1	(1.9)	3	(5.7)	2	(3.8)	2	(3.8)	8	(3.8)	0.959
Decreased appetite	1	(1.9)	2	(3.8)	1	(1.9)	0	(0.0)	4	(1.9)	0.711
Dehydration	2	(3.8)	0	(0.0)	0	(0.0)	0	(0.0)	2	(1.0)	0.121
Dental caries	0	(0.0)	2	(3.8)	1	(1.9)	0	(0.0)	3	(1.4)	0.524
Dermal cyst	0	(0.0)	1	(1.9)	0	(0.0)	0	(0.0)	1	(0.5)	1.000
Dermatitis contact	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)	1	(0.5)	1.000
Diarrhoea	2	(3.8)	2	(3.8)	5	(9.6)	7	(13.2)	16	(7.6)	0.210
Dizziness	1	(1.9)	1	(1.9)	1	(1.9)	2	(3.8)	5	(2.4)	1.000
Dry eye	0	(0.0)	1	(1.9)	0	(0.0)	0	(0.0)	1	(0.5)	1.000
Dry skin	0	(0.0)	1	(1.9)	1	(1.9)	0	(0.0)	2	(1.0)	0.872
Duchenne muscular dystrophy	1	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0.495
Dysgeusia	1	(1.9)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)	0.495
Dyspepsia	0	(0.0)	1	(1.9)	2	(3.8)	0	(0.0)	3	(1.4)	0.335
Dyspnoea	0	(0.0)	0	(0.0)	0	(0.0)	1	(1.9)	1	(0.5)	1.000
ECG signs of ventricular hypertrophy	0	(0.0)	0	(0.0)	1	(1.9)	0	(0.0)	1	(0.5)	0.495

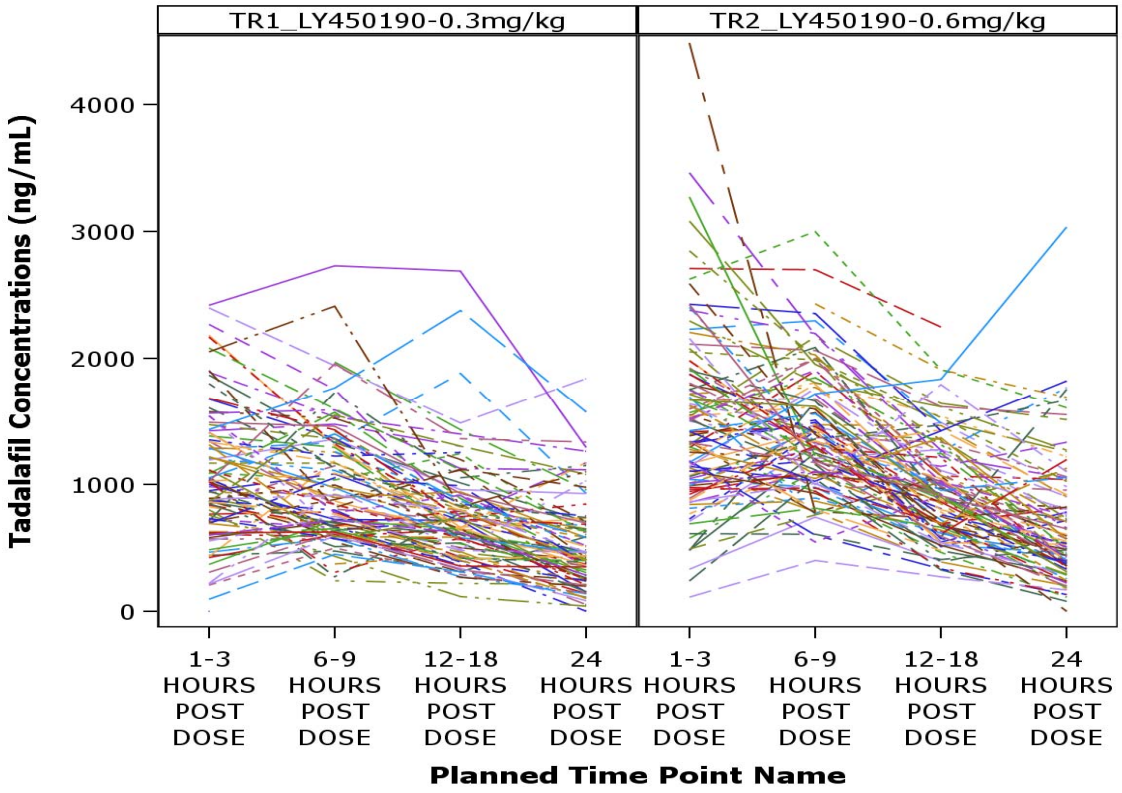
Abbreviations: AUC = area under concentration and time curve; n = number of patients with at least one treatment-emergent adverse event per category; N = number of patients in the safety analysis set with non-missing PK data; TEAE = treatment-emergent adverse event.
All percentages are based on the safety analysis set.
[a] Using Fisher's exact test to test whether the proportions of each TEAE category are the same among the 4 AUC quartiles.
MedDRA Version 18.1

Source: Table LVJJ.14.103 on Page 937 in lvjj-04-body.pdf (Shown here is one of the tables as provided by the Applicant)

OCP's Comments

Fulfilled as stated in PWR

The reviewer conducted graphical analysis to understand the data collected to describe the pharmacokinetics of tadalafil. Adequate data has been collected that helps to describe the PK profile using a one-compartment model.



Source: Reviewer's Analysis

No independent exposure-response analysis was conducted by the Agency. Since the study failed to demonstrate any benefit from the two studied doses of tadalafil, no discernable relationship between AUC and change in 6MWD is expected. The reporting of safety results by AUC quartiles of tadalafil is acceptable.

Written Request Item #3: Age-Appropriate Formulation

Bioavailability of any formulation used in the studies must be characterized, and as needed, a relative bioavailability study comparing the approved drug to the age appropriate formulation may be conducted in adults.

Information Submitted/ Applicant's response

The Applicant did not develop a new pediatric formulation for Study LVJJ, as per EMEACHMP Reflection Paper *Formulation of Choice for the Pediatric Population* dated 21 September 2006, tadalafil tablets are considered of appropriate size for dosing in the pediatric patients age 7-14 years.

Study Drug	Strength	Formulation	Source
Tadalafil	2.5 mg	tablet	Lilly del Caribe, Inc.
	5 mg	tablet	Puerto Rico Industrial Park
	10 mg	tablet	12.6 KM 65th Infantry Road
	20 mg	tablet	Carolina, Puerto Rico 00985, USA
Placebo	not applicable	tablet	Fisher Clinical Services, Inc. Lilly Technology Center Indianapolis, Indiana 46221, USA

Source: Table LVJJ.9.2 on Page 49 in lvjj-04-body.pdf

The total daily tadalafil dose for each weight category was achieved with a combination of existing tadalafil tablet strengths (2.5, 5, 10, and 20 mg) or matching placebo tablets. The dosing algorithm used in the study is shown below.

Table LVJJ.9.1. Dosing Algorithm by Weight Category and Tadalafil Target Dose

Weight (kg)	Tadalafil 0.3 mg/kg/day	Tadalafil 0.6 mg/kg/day
<20	5 mg	10 mg
20 to <25	7.5 mg	15 mg
25 to <30	10 mg	17.5 mg
30 to <35	10 mg	20 mg
35 to <40	12.5 mg	22.5 mg
40 to <50	15 mg	30 mg
50 to <60	17.5 mg	35 mg
≥60	20 mg	40 mg

Source: LVJJ protocol.

Source: Table LVJJ.9.1 on Page 49 in lvjj-04-body.pdf

OCP's Comments

Fulfilled as stated in PWR

Since the approved formulations are used in the study, no additional bioavailability studies are required.

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/s/

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