EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 March 2017
EMA/752183/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Adcirca / Cialis

International non-proprietary name: tadalafil

Procedure No. EMEA/H/C/WS1066

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Eli Lilly Nederland B.V. submitted to the European Medicines Agency on 21 October 2016 an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I

Update of sections 4.2 and 5.1 of the SmPC in order to reflect the results of study H6D-MC-LVJJ, a randomized, double-blind, placebo-controlled phase 3 trial of tadalafil in the treatment of Duchenne Muscular Dystrophy (DMD), to fulfil Adcirca P46 019.1 and Cialis P46 045.1.

The requested worksharing procedure proposed amendments to the Summary of Product Characteristics.

1.2. Rationale for the proposed change

The MAH submitted in May 2016 the final clinical study report for study H6D-MC-LVJJ for Adcirca and Cilais in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended. Study H6D-MC-LVJJ was a randomized, double-bind, placebo-controlled, phase 3 trial of tadalafil for duchenne muscular dystrophy (DMD). Study LVJJ was a 3-arm study of placebo, tadalafil 0.3 mg/kg, and 0.6 mg/kg daily in paediatric patients 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). The primary objective was 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 boys with DMD. The efficacy outcomes of the study were negative with no effect demonstrated in slowing the decline in ambulation as measured by the primary 6MWD endpoint or any of the secondary endpoints. Therefore, no recommendations for the use of tadalafil in this population can be made and no updates to the Summary of Product Characteristics (SmPC) were suggested.

Although it was acknowledged that the efficacy or safety results of this study do not impact the benefit-risk assessment for currently approved indications in adults, the CHMP requested the MAH to submit a variation to update sections 4.8, 5.1 and 5.2 of the SmPC following their assessment of the Article 46 procedure (EMA/H/C/000436/P46-045 and EMEA/H/C/001021/P46-019). The MAH therefore submitted the requested type II variation with a proposal to update the Cialis and Adcirca SmPCs with the results of study H6D-MC-LVJJ.

2. Overall conclusion and impact on the benefit/risk balance

Tadalafil is a selective inhibitor of the phosphodiesterase type 5 (PDE5) enzyme. Tadalafil was approved for the treatment of men with erectile dysfunction (ED) dosed either as needed or once daily and to treat patients with signs and symptoms of benign prostatic hyperplasia (BPH; dosed once daily) under the brand name Cialis. Tadalafil was also approved to treat patients with pulmonary arterial hypertension (PAH, dosed once daily) under the brand name Adcirca.

Tadalafil was considered to have a role in muscle function in duchenne muscular dystrophy (DMD). Non-clinical and early clinical studies suggested that relief of microvascular ischemia could reduce use-dependent injury of skeletal muscle, slowing disease progression and slowing the decline in walking ability.

The efficacy and safety of tadalafil as a treatment for ambulatory DMD patients was evaluated in a randomized, double-blind, placebo-controlled, multicentre clinical study with 0.3 mg/kg and 0.6 mg/kg daily dose for 48 weeks. The efficacy outcomes of the study were negative with no effect demonstrated in slowing the decline in ambulation as measured by the primary 6MWD endpoint or any of the secondary endpoints.

Although it was acknowledged that the efficacy or safety results of this study do not impact the benefit-risk assessment for currently approved indications in adults, the CHMP requested the MAH to submit a variation to update sections 4.8, 5.1 and 5.2 of the SmPC following the assessment of the Article 46 procedure (EMA/H/C/000436/P46 045 for Cialis and EMEA/H/C/001021/P46 019 for Adcirca) which concluded in August 2016. The MAH therefore submitted this WS application and proposed to update only sections 4.2 and 4.8 of the SmPC for Cialis and Adcirca. The MAH is of the opinion that no information should be included in sections 4.8 and 5.2 of the SmPC in order to avoid misleading messages to prescribers and to minimise the potential to encourage or provide justification for off-label use. It is acknowledged that an unjustified off-label use of medicinal products in paediatric population should be avoided. Initially, the MAH was requested as part of the request for supplementary information to provide PK information available from 210 paediatric patients as it was considered sufficiently relevant to be reflected in the SmPC. After further discussion, the CHMP concluded that section 5.2 of the SmPC could remain unchanged and that no PK data needed to be included in section 5.2 of the SmPC from study H6D-MC-LVJJ in children with DMD.

Overall, based on the data presented the benefit-risk balance of Cialis and Adcirca remains positive in the current approved indication in adult. The safety and efficacy of Adcirca in the paediatric population remains to be established. Available paediatric data are described in section 5.1 of the Adcirca and Cialis SmPC.

Scientific Summary for the EPAR

Please refer to the published assessment report EMEA/H/C/WS/1066: EPAR - Assessment Report – Variation

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation accepted		Type	Annexes affected
C.I.3.b	C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH	Type II	I and II

Update of sections 4.2 and 5.1 of the Adcirca SmPC and update of section 5.1 of the Cialis SmPC in order to reflect the results of study H6D-MC-LVJJ, a randomized, double-blind, placebo-controlled phase 3 trial of tadalafil in the treatment of Duchenne Muscular Dystrophy (DMD), to fulfil Adcirca P46 019.1 and Cialis P46 045.1. In addition the MAH took the opportunity to update section 6.6 of the SmPC to remove the statement 'no special requirements' for Adcirca and Cialis and to add the standard statement about disposal of any unused or waste material for Cialis, and to align annex II.C with the latest QRD template version 10.

☒ is recommended for approval by consensus .

The worksharing procedure leads to amendments to the Summary of Product Characteristics and to the Annex II.

4. Scientific discussion

4.1. Introduction

Eli Lilly and Company (Lilly) recently submitted on 20 May 2016 a completed paediatric clinical study report for Cialis (tadalafil) and Adcirca (tadalafil), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended. The report related to study H6D-MC-LVJJ (LVJJ), a randomized, double-blind, placebo-controlled, phase 3 trial of tadalafil for Duchenne Muscular Dystrophy (DMD). Study LVJJ was a 3-arm study of placebo, tadalafil 0.3 mg/kg, and 0.6 mg/kg daily in paediatric patients 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). The primary objective was 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 boys with DMD.

The efficacy outcomes of the study were negative with no effect demonstrated in slowing the decline in ambulation as measured by the primary 6MWD endpoint or any of the secondary endpoints. Therefore, no recommendations for the use of tadalafil in this population can be made and no updates to the Summary of Product Characteristics (SmPC) were suggested.

Although it was acknowledged that the efficacy or safety results of this study do not impact the benefit-risk assessment for currently approved indications in adults, the CHMP requested the MAH to submit a variation to update sections 4.8, 5.1 and 5.2 of the SmPC following their assessment of the Article 46 procedure (EMA/H/C/000436/P46 045 for Cialis and EMEA/H/C/001021/P46 019 for Adcirca) which concluded in August 2016. The CHMP concluded that the inclusion of (lack of) efficacy data from a negative study will prevent from prescribing an inefficacious treatment and that the description of the safety profile and pharmacokinetic characterisation of tadalafil in children and adolescent is also of relevance.

This application presents the MAH's proposed wording for updating the Cialis and Adcirca SmPCs. The proposed wording described in the following sections aims to provide clinically relevant data for prescribers while maintaining a clear message that tadalafil is not recommended for use in paediatric patients at this time.

4.2. Clinical Efficacy aspects

Study H6D-MC-LVJJ (a randomized, double-blind, placebo-controlled, phase 3 trial of tadalafil for Duchenne Muscular Dystrophy)

Description

Study LVJJ is a phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel, 3-arm study of tadalafil 0.3 mg/kg and 0.6 mg/kg daily in patients with DMD who were being treated with corticosteroids. The study consisted of a 48-week double-blind treatment period, followed by an OLE.

Methods

Objectives

The primary objective was 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 boys with DMD.

The secondary objectives were to test the hypothesis that once-daily tadalafil administered orally for 48 weeks compared with placebo in boys with DMD:

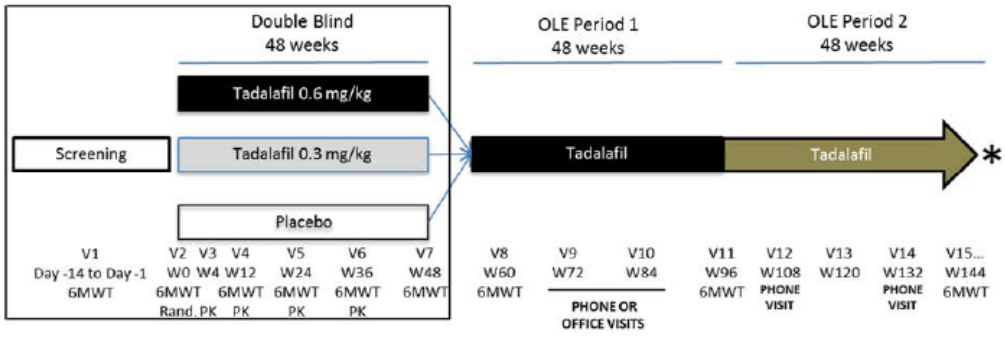
- lessened the decline in North Star Ambulatory Assessment (NSAA) global score;
- lessened the decline in performance on timed function tests (rise from floor from supine, 10 meter walk/run, stair climb, and stair descend);
- delayed the time to persistent 10% worsening in the 6MWD or the timed function tests;
- 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)
- characterize the pharmacokinetics (PK) of tadalafil in pediatric DMD patients, and assess relationships between tadalafil exposure and efficacy and safety outcomes.

Exploratory objectives included assessing the decline in upper limb performance, decline in pulmonary function and reduced resting heart rate.

Study design

It is a Phase 3, multicentre, randomised, double-blind, placebo-controlled, parallel, 3-arm study.

Study LVJJ included both a double-blind treatment period and an OLE phase.



Abbreviations: 6MWT = 6-minute walk test; CSR = clinical study report; OLE = open-label extension; PK = pharmacokinetic sampling; Rand = randomization; V = visit; W = study week.
The 48-week double-blind treatment period (boxed) is presented in this CSR (Visit 2 through Visit 7).
Not all functional assessments for each visit are shown, only the 6MWT (see Table LVJJ.9.3). Adverse events were collected at every visit. Dosing instructions in OLE periods are available in the protocol located in the Protocol and Addenda appendix.
*Patients that completed Visit 15 (Week 144) were to continue receiving tadalafil and have study visits every 3 months until 1 of 2 criteria were met (see study protocol for details).

Study population /Sample size

The study population consisted of males of 7-14 years of age with proven DMD (as defined by typical clinical presentation plus muscle biopsy that showed near-complete dystrophin deficiency or genetic confirmation), who were ambulant (6MWD between 200 and 400 meters) and showed a left ventricular ejection fraction (LVEF) ≥ 50%. Patients were receiving systemic corticosteroids for a minimum of 6 months immediately prior to screening.

The study was powered to detect a between-group difference in mean change score in 6MWD distance of 30 meters. Assuming a common standard deviation of 60 meters, 102 patients would provide 90% power to detect a placebo-adjusted difference of 30 meters in changes in 6MWD for each tadalafil dose group, resulting in a total of 306 patients planned to be enrolled into the study with a 1:1:1 ratio among the 3 arms.

Treatments

During the double-blind treatment period, patients were randomized to receive 1 of 2 target doses of tadalafil (0.3 mg/kg or 0.6 mg/kg) or matching placebo orally once daily for 48 weeks.

Outcomes / endpoints

- The primary endpoint was the change from baseline in 6-minute walk distance (6MWD) at 48 weeks.
- Secondary Efficacy Measures
    - North Star Ambulatory Assessment (NSAA)
    - Timed Function Tests: rise from floor from supine position, 10 meter walk/run, and 4-stair climb and descend timed function tests.

- Quality of Life Measure: Pediatric Outcomes Data Collection Instrument (PODCI)
- Exploratory Efficacy Measures: Performance of the Upper Limb (PUL) Scale; Pulmonary Function Testing; Heart Rate.

Statistical Methods

All tests of treatment effects were conducted at a 2-sided significance level of 0.05, with the exception of the planned testing structure of the primary objective and confirmatory secondary objectives. Confirmatory testing of 5 secondary objectives was to be conducted only if both null hypotheses for the primary objective were rejected.

Efficacy analyses were conducted on the full analysis set (FAS) on an intention-to-treat (ITT) basis. This set included all data from all randomized patients according to the treatment the patients were assigned, even if the patient never took the assigned treatment or did not receive the correct treatment. For the double-blind treatment period, baseline for efficacy and safety analyses was the last non-missing observation prior to the first dose; the endpoint for these analyses was Visit 7 with the exception of a few analyses that used last observation as endpoint.

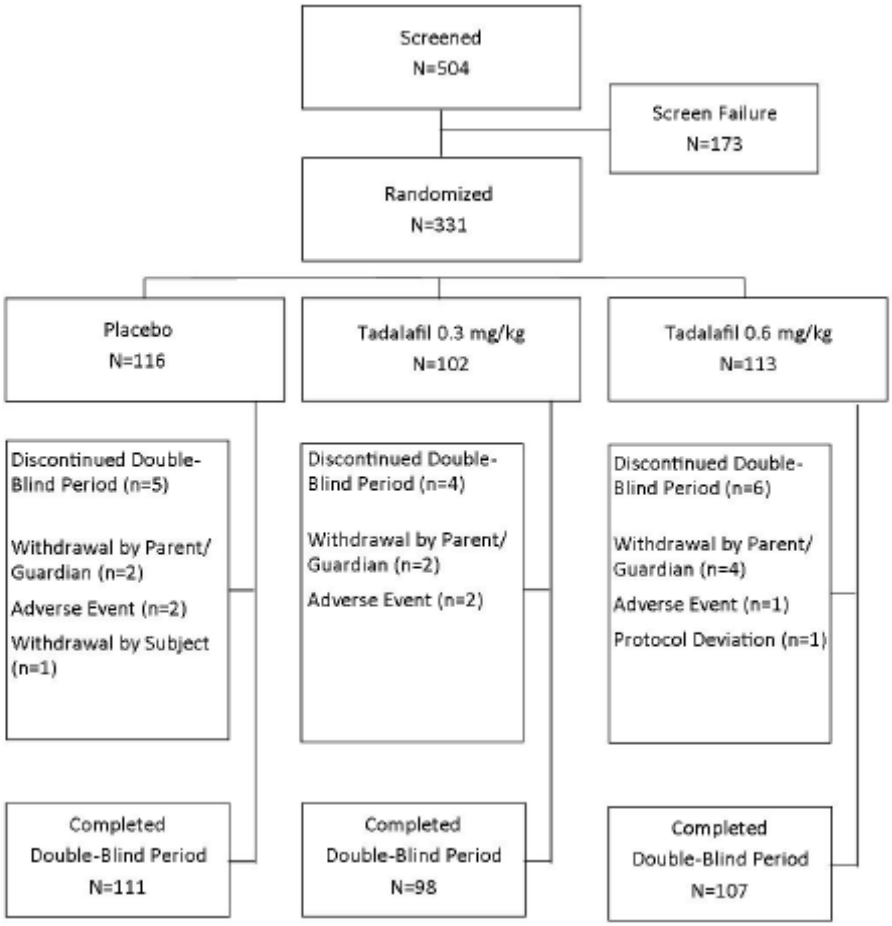
An interim analysis was performed to assess potential futility; the data cut-off point was when approximately 50% of enrolled patients completed their involvement with the double-blind period (either completed the period or discontinued early).

Results

Recruitment / Number analysed

A total of 504 patients were screened, 331 patients were randomised, and 316 patients completed the study.

Patient disposition



Sources: Table LVJJ.14.1 and Table LVJJ.10.1.

Baseline data

The treatment groups were generally balanced with regard to most demographic characteristics. The mean age of patients was 9.6 years. Patients 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 patients >10 years of age (32.4%) compared to the placebo group (17.2%) and the tadalafil 0.6 mg/kg group (19.5%).

The majority of patients were White (79.2%). Mean 6MWD at baseline was 329 meters (54% of the predicted value for age and height). Mean 6MWD scores at baseline were 335.0 meters, 324.2 meters, and 327.8 meters in the placebo, tadalafil 0.3 mg/kg, and tadalafil 0.6 mg/kg treatment groups, respectively. The majority of patients had baseline 6MWD ≥ 300 meters (74.3%).

On the rise from floor timed function test, mean time in the placebo treatment group was 8.4 seconds, compared to 9.6 seconds and 10.2 seconds in the tadalafil 0.3 mg/kg and tadalafil 0.6 mg/kg treatment groups, respectively. Moreover, the proportion of patients unable to perform the rise from floor task independently at baseline was higher in the tadalafil 0.3 mg/kg group (30.4%) compared with the placebo group (22.4%) and the tadalafil 0.6 mg/kg group (25.7%).

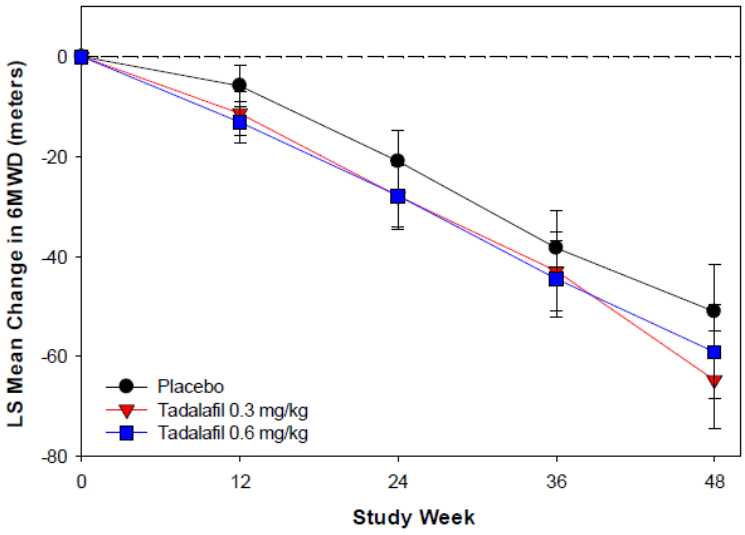
All patients were taking a corticosteroid at baseline, either prednisone/prednisolone (53.8%) or deflazacort (45.9%). The proportion of patients reporting use of deflazacort during the study was higher in the placebo group (51.7%) compared with the tadalafil 0.3 mg/kg group (42.2%) and the tadalafil 0.6 mg/kg group (45.1%). Mean duration of corticosteroid therapy was 40.6 months at baseline, and most patients (71.9%) were taking a daily corticosteroid regimen.

Mean compliance across all treatment groups exceeded 97% at each visit, with no appreciable difference between treatment groups.

Efficacy results

Primary Efficacy – 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: least squares (LS) mean change in 6MWD at 48 weeks was -51.0 meters (m) in the placebo group, compared with -64.7m in the tadalafil 0.3 mg/kg group (p=.307) and -59.1m in the tadalafil 0.6 mg/kg group (p=.538).



Abbreviations: 6MWD = 6-minute walk distance; LS = least squares; SE = standard er
Source: Table LVJJ.14.21.

Figure LVJJ.11.1. LS mean change (±SE) from baseline in 6MWD by study week.

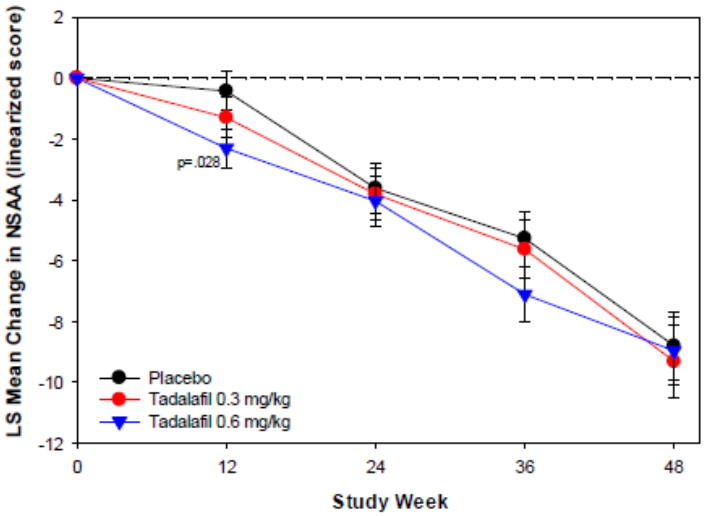
Secondary Efficacy Analysis

There was also no evidence of efficacy of tadalafil in analysis of 6MWD expressed as a percent change from baseline. The LS mean percent decrease in 6MWD from baseline to Week 48 was 17.3%, 23.3%, and 20.8% in the placebo, tadalafil 0.3 mg/kg, and tadalafil 0.6 mg/kg treatment groups, respectively.

There was no significant difference in the survival curves for persistent 10% worsening in 6MWD between treatments. By 48 weeks, 37.9% of patients in the placebo group experienced persistent 10% worsening in 6MWD, compared with 37.3% in the tadalafil 0.3 mg/kg group and 44.2% in the tadalafil 0.6 mg/kg group. Thirty-two (9.7%) patients lost ambulation by 48 weeks: 7 (6.0%) in the placebo group, compared to 16 (15.7%) in the tadalafil 0.3 mg/kg group (p=.027) and 9 (8.0%) in the tadalafil 0.6 mg/kg group (p=.613).

No evidence of efficacy on the 6MWD was observed in prespecified subgroup analysis based on baseline ambulation category (6MWD <300 meters versus ≥ 300 meters), corticosteroid type (prednisone/prednisolone versus deflazacort), or frequency of corticosteroid regimen (daily versus non-daily).

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 linearised 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).



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

Figure LVJJ.11.4. LS mean change (±SE) from baseline in NSAA (linearized score) by study week.

Consistent with DMD disease progression, functional performance on all of the timed function tests (rise from floor from supine, 10 meter walk/run, stair climb, and stair descend) 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.

Functional QoL 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 both 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.

Exploratory Efficacy Measures

- There was no significant effect of tadalafil treatment on the PUL total score or any individual PUL domain score, with the exception of a statistically significant 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.
- Changes in absolute and percent-predicted values for pulmonary function tests (FVC, FEV1, PEF, and FEV1/FVC ratio) from baseline to endpoint also were small with no clinically meaningful treatment group differences.

- 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.

Pharmacokinetic/Pharmacodynamic Analyses

The PopPK dataset included data from 210 patients whose ages ranged from 7 to 14 years and who weighed 14.5 to 76.3 kg at study entry. Age and body weight were well-balanced between the treatment groups. Patients in the 0.6 mg/kg treatment group tended to receive higher doses than did those in the 0.3 mg/kg treatment group.

Table LVJJ.11.22. Demographics at Study Entry for Patients Included in the Pharmacokinetic Analysis

Tadalafil Treatment Group	Age (yr)	Body Weight (kg)
0.3 mg/kg		
Arithmetic mean (CV)	9.54 (23.0%)	34.2 (34.8%)
Range	7 – 14	16.5 – 76.3
n	100	100
0.6 mg/kg		
Arithmetic mean (CV)	9.15 (19.0%)	32.0 (35.1%)
Range	7 – 14	14.5 – 70.6
n	110	110

Abbreviations: CV = coefficient of variation; n = number of patients included in the pharmacokinetic analysis for each treatment; yr = years.

The AUC of tadalafil was not dose-proportional between the 0.3 mg/kg and 0.6 mg/kg treatment groups. As the dose doubled from 0.3 mg/kg to 0.6 mg/kg, the population steady-state AUC increased only 43% from 6550 ng·hr/mL to 9380 ng·hr/mL. This likely reflects the fact that patients in the lower-dose group received doses of ≤20 mg, which is the linear range in adults, whereas many patients in the higher-dose group received doses above 20 mg.

Tadalafil exposures were within the range of those estimated during the recommended once-daily starting-dose regimens for approved treatments of ED, BPH, and PAH in adults.

Table LVJJ.11.26. Individual-predicted AUC of Tadalafil at Steady State

Tadalafil Treatment Group	AUC_{ss} (ng•hr/mL)
0.3 mg/kg	
Geometric Mean (CV)	6550 (42.7%)
Range	2283 – 18762
n	100
0.6 mg/kg	
Geometric Mean (CV)	9380 (35.6%)
Range	3468 – 21249
n	110

Abbreviations: AUC_{ss} = area under the curve of concentration versus time at steady state; CV = geometric coefficient of variation; n = total number of patients included in the pharmacokinetic analysis for the treatment group.

4.3. Safety aspects

Safety: 48-Week Double-blind Treatment Period

Of the 331 randomized patients, 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 patients were also receiving corticosteroids throughout the study and 96.4% received ≥ 1 concomitant medication in addition to corticosteroids.

The results showed no significant between treatment group differences in the proportion of patients reporting ≥ 1 TEAE, SAE, discontinuation due to AE, DMD-related TEAE, corticosteroid-related TEAE, or procedure-related TEAE, and there were no deaths reported.

Table LVJJ.12.3. Overview of Adverse Events
Double-Blind Treatment Period
Safety Analysis Set

Adverse Event [a]	Placebo (N=116) n	(%)	Tadalafil 0.3mg/kg (N=102) n	(%)	p-value [b]	Tadalafil 0.6mg/kg (N=112) n	(%)	p-value [b]	Total (N=330) n	(%)
Deaths [c]	0	(0.0)	0	(0.0)		0	(0.0)		0	(0.0)
Serious Adverse Events	5	(4.3)	4	(3.9)	1.000	6	(5.4)	0.765	15	(4.5)
Adverse Events Leading to Discontinuation	2	(1.7)	2	(2.0)	1.000	1	(0.9)	1.000	5	(1.5)
Treatment-Emergent Adverse Events [d]	101	(87.1)	90	(88.2)	0.839	97	(86.6)	1.000	288	(87.3)
Treatment-Related Adverse Events	48	(41.4)	51	(50.0)	0.222	67	(59.8)	0.006	166	(50.3)
Study Disease-Related Adverse Events	47	(40.5)	46	(45.1)	0.583	44	(39.3)	0.893	137	(41.5)
Procedure-Related Adverse Events	9	(7.8)	4	(3.9)	0.266	3	(2.7)	0.136	16	(4.8)
Adjunct Treatment Related Adverse Events [e]	23	(19.8)	13	(12.7)	0.201	17	(15.2)	0.388	53	(16.1)

Abbreviations: n = number of patients per category; N = number of patients in the safety analysis set.
All percentages are based on the safety analysis set.
[a] Patients may be counted in more than one category.
[b] P-values are from Fisher's exact tests comparing each of the treatment groups versus placebo.
[c] Deaths are also counted as serious adverse events and as adverse events leading to discontinuation.
[d] Treatment-emergent adverse events are defined as events that are new or worsening since first dose of study drug.
[e] Adjunct treatment refers to corticosteroid therapy.
MedDRA Version 18.1

There was a significantly greater proportion of patients with ≥ 1 TEAE assessed by the investigator as related to study treatment in the tadalafil 0.6 mg/kg group compared with placebo (59.8% versus 41.4%, p=.006), with the difference largely due to significantly more patients with treatment-related TEAEs of erection increased and spontaneous penile erection in the tadalafil 0.6 mg/kg group versus placebo. Of note, 41.5% and 16.1% of patients across all treatment groups reported TEAEs assessed by the investigator as related to DMD and/or to corticosteroid use, respectively.

Table LVJJ.12.5. Treatment-Emergent Adverse Events Occurring in at Least 5% of Patients in Either Tadalafil Treatment Group by Preferred Term
Double-Blind Treatment Period
Safety Analysis Set

MedDRA Preferred Term	Placebo N = 116 n (%)	Tadalafil 0.3 mg/kg N = 102 n (%)	p-value	Tadalafil 0.6 mg/kg N = 112 n (%)	p-value
Patients with ≥1 TEAE	101 (87.1)	90 (88.2)	.839	97 (86.6)	1.00
Headache	36 (31.0)	39 (38.2)	.317	43 (38.4)	.267
Fall	25 (21.6)	18 (17.6)	.499	23 (20.5)	.872
Nasopharyngitis	16 (13.8)	7 (6.9)	.123	18 (16.1)	.711
Erection increased	3 (2.6)	9 (8.8)	.071	17 (15.2)	<.001
Vomiting	14 (12.1)	6 (5.9)	.158	17 (15.2)	.564
Spontaneous penile erection	4 (3.4)	13 (12.7)	.012	13 (11.6)	.023
Upper respiratory tract infection	10 (8.6)	10 (9.8)	.817	12 (10.7)	.657
Diarrhoea	10 (8.6)	6 (5.9)	.604	10 (8.9)	1.000
Pain in extremity	8 (6.9)	6 (5.9)	.790	10 (8.9)	.629
Pyrexia	5 (4.3)	11 (10.8)	.075	10 (8.9)	.188
Abasia	7 (6.0)	14 (13.7)	.067	9 (8.0)	.611
Abdominal pain	6 (5.2)	4 (3.9)	.753	9 (8.0)	.432
Abdominal pain upper	7 (6.0)	5 (4.9)	.774	8 (7.1)	.794
Flushing	3 (2.6)	8 (7.8)	.119	8 (7.1)	.131
Back pain	9 (7.8)	11 (10.8)	.487	7 (6.3)	.797
Epistaxis	5 (4.3)	10 (9.8)	.178	6 (5.4)	.765
Influenza	9 (7.8)	8 (7.8)	1.00	5 (4.5)	.410
Nausea	2 (1.7)	7 (6.9)	.086	3 (2.7)	.679

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Source: Table LVJJ.14.101.

Spontaneous penile erection and erection increased were the only individual preferred term events reported by significantly higher proportions of patients in the tadalafil groups compared with placebo. All of the events were reported as mild or moderate in severity and none led to discontinuation. The TEAEs related to penile erection are consistent with the known pharmacodynamics of tadalafil and no events of priapism were reported.

Most of the individual SAEs reported were consistent with the type of events expected for patients with DMD taking corticosteroids and the most frequently reported SAEs were falls, fractures, and infections. One patient in the tadalafil 0.3 mg/kg group reported an SAE of myocarditis that led to study discontinuation.

Table LVJJ.12.6. Serious Adverse Events
Double-Blind Treatment Period
Safety Analysis Set

Preferred Term	Placebo (N=116)		Tadalafil 0.3mg/kg (N=102)			Tadalafil 0.6mg/kg (N=112)			Total (N=330)	
	n	(%)	n	(%)	p-value [a]	n	(%)	p-value [a]	n	(%)
Patients with >= 1 SAE	5	(4.3)	4	(3.9)	1.000	6	(5.4)	0.765	15	(4.5)
Fall	1	(0.9)	0	(0.0)	1.000	2	(1.8)	0.617	3	(0.9)
Femur fracture	0	(0.0)	0	(0.0)		2	(1.8)	0.240	2	(0.6)
Pharyngotonsillitis	0	(0.0)	0	(0.0)		1	(0.9)	0.491	1	(0.3)
Pneumonia adenoviral	0	(0.0)	0	(0.0)		1	(0.9)	0.491	1	(0.3)
Tendinous contracture	1	(0.9)	0	(0.0)	1.000	1	(0.9)	1.000	2	(0.6)
Varicella	0	(0.0)	0	(0.0)		1	(0.9)	0.491	1	(0.3)
Abasia	1	(0.9)	0	(0.0)	1.000	0	(0.0)	1.000	1	(0.3)
Bronchitis	1	(0.9)	0	(0.0)	1.000	0	(0.0)	1.000	1	(0.3)
Femoral neck fracture	1	(0.9)	0	(0.0)	1.000	0	(0.0)	1.000	1	(0.3)
Gastrointestinal infection	0	(0.0)	1	(1.0)	0.468	0	(0.0)		1	(0.3)
Lower limb fracture	1	(0.9)	0	(0.0)	1.000	0	(0.0)	1.000	1	(0.3)
Muscle contracture	0	(0.0)	1	(1.0)	0.468	0	(0.0)		1	(0.3)
Myocarditis	0	(0.0)	1	(1.0)	0.468	0	(0.0)		1	(0.3)
Pneumonia	0	(0.0)	1	(1.0)	0.468	0	(0.0)		1	(0.3)

Abbreviations: n = number of patients with at least one serious adverse event per category;
N = number of patients in the safety analysis set; SAE = serious adverse event.
All percentages are based on the safety analysis set.
[a] P-values are from Fisher's exact tests comparing each of the treatment groups versus placebo.
MedDRA Version 18.1

Analyses of TEAEs by AUC quartiles in the tadalafil groups combined did not show a consistent pattern of increased TEAEs with increasing concentrations of tadalafil. There was a significant difference among the quartiles for the TEAE of spontaneous penile erection with a higher proportion of patients reporting events in the lower versus the upper AUC quartiles. Headache was the only TEAE with a significant difference among the AUC quartiles in which the fourth quartile had a higher proportion of patients reporting events compared with the 3 lower quartiles.

There were no significant between-group differences in the proportion of patients reporting ≥ 1 TEAE of headache in either tadalafil group compared with placebo. There were no clinically meaningful differences in laboratory parameters from baseline to endpoint between the tadalafil and placebo groups when analyzed as mean change or as categorical change (ie, abnormal, low, and high). There were also no significant between-group differences in laboratory-related TEAEs. The criteria for elevated hepatic laboratory results were met by 3 patients (1 placebo, 2 tadalafil 0.3 mg/kg). One tadalafil patient with pre-existing Gilbert's syndrome had elevated bilirubin at baseline and all postbaseline visits, and the other 2 patients met criteria for increased ALT at a single postbaseline visit. Hepatic enzyme increased was reported as a TEAE by the patient in the placebo group.

Tadalafil did not have clinically meaningful effects compared with placebo on mean changes or categorical changes in blood pressure or pulse rate through 48 weeks. At some study time points, there were significant differences in the mean change in systolic and/or diastolic pressure between the tadalafil groups and placebo, but the effects were not persistent and likely reflect the known mild vasodilatory effect of PDE5 inhibition. There were no significant differences between treatment groups in the proportion of patients that reported TEAEs that may have been related to hypotension, including dizziness and falls. No events of syncope were reported during the double-blind treatment period.

Changes in height and weight in the tadalafil groups through 48 weeks were not significantly different from placebo.

There were no clinically meaningful differences between the tadalafil groups versus placebo in LVEF and shortening fraction measured by serial echocardiograms, LVEF and circumferential wall strain as measured by MRI in a subgroup of 27 patients, changes in quantitative ECG parameters, and the occurrence of treatment-emergent qualitative ECG abnormalities as determined by central evaluation. The most frequent (>10% overall) treatment emergent qualitative ECG abnormalities in all treatment groups were rhythm and conduction abnormalities with no significant differences between groups. Electrocardiogram abnormalities were also common at baseline (27.9% of patients overall had rhythm disturbances and 43.3% had conduction abnormalities) and thus, were not unexpected in this population.

The echocardiogram measures of LV internal diameter (systole and diastole) showed small mean increases from baseline to 24 weeks and to 48 weeks in the tadalafil groups and placebo group, with significantly larger increases in the tadalafil groups compared with placebo at some time points. The MRI results showed mean increases from baseline to 48 weeks in LVEDV and LVESV in the tadalafil groups and placebo group, with the mean change in LVEDV significantly greater in the tadalafil 0.3 mg/kg group versus placebo (p=.047). Mean changes in stroke volume, cardiac output, and LV mass from baseline to 48 weeks were numerically greater in the tadalafil groups compared with placebo. Cardiac related AEs (eg, right and left ventricular hypertrophy) were reported at a low frequency (ie, 1 to 2 patients) with no significant difference between treatment groups.

Few patients had clinically significant abnormal eye exams at Week 48 (3 placebo, 5 tadalafil 0.6 mg/kg). Most TEAEs in the SOC Eye Disorders were mild in severity and 1 event of mild visual impairment in the placebo group led to discontinuation. Adverse events such as increased intraocular pressure (1 patient in tadalafil 0.6 mg/kg group), optic nerve cupping (1 patient in tadalafil 0.6 mg/kg group), and cataract (1 placebo patient) are not unexpected in patients receiving chronic corticosteroid therapy (Liu et al. 2013).

In summary, the overall safety profile in Study LVJJ was generally consistent with the known safety profile of tadalafil and with AEs expected in a pediatric DMD population receiving corticosteroids. The only TEAEs with a significant difference between groups were erection increased and spontaneous penile erection and these events were expected based on the known pharmacodynamic effects of PDE5 inhibition. There were no significant differences between groups in the proportion of patients reporting SAEs or who discontinued the study due to AEs.

Although some changes in cardiac function measured by MRI and echocardiogram related to increases in LV volumes were greater in the tadalafil groups compared with placebo, the changes were small, and all other assessments of cardiac function, including LVEF by MRI and echocardiogram, were similar between the tadalafil and placebo groups.

Interim 6-month OLE Treatment Period

Patients that completed the double-blind treatment period could participate in an OLE for up to 96 weeks. An interim clinical study report summarising the safety data collected for up to 6 months into the OLE has been completed (submission cutoff date of 16 December 2015). A total of 234 patients contributed data to the interim 6-month OLE safety analysis. All patients in the OLE received tadalafil once daily (0.3 mg/kg (n= 111 [including 70 who received 0.3 mg/kg in the double-blind period]) or 0.6 mg/kg (n=123 [including 79 who received 0.6 mg/kg in the double-blind period]).

Eight patients reported 9 SAEs, with none of the events considered by the investigator to be related to study drug (3 [2.7%] all tadalafil 0.3 mg/kg, 5 [4.1%] all tadalafil 0.6 mg/kg). Most of the individual SAEs reported were consistent with the type of events expected for patients with DMD taking corticosteroids. The most frequently reported SAEs were related to infection (n=4) and there was 1 SAE of fracture. One patient in the all tadalafil 0.6 mg/kg group with preexisting psychiatric disorders reported SAEs of self-injurious behaviour and suicidal ideation. No deaths were reported and no patient discontinued due to ≥ 1 AE.

The most common TEAEs (≥5% of patients) reported in the interim 6-month OLE were similar to those reported by ≥5% in either tadalafil group in the double-blind period and included fall, abasia, back pain, erection increased, pyrexia, and vomiting. The proportion of patients with ≥ 1 TEAE assessed by the investigators as related to study drug was 12.4% (29/234). Similar to that observed in the double-blind phase, the investigators also assessed many of the TEAEs in the interim 6-month OLE as related to the DMD disease state (18.8%) and/or to corticosteroid use (4.2%).

Table LVJJ.8.4. Treatment-Emergent Adverse Events Occurring in at Least 5% of Patients in Any Treatment Group by Preferred Term OLE Treatment Period 6-Month Open-Label Data

MedDRA Preferred Term	0.3/Placebo N=41 n[a] (%)	0.3/0.3 N=70 n[a] (%)	0.6/Placebo N=44 n[a] (%)	0.6/0.6 N=79 n[a] (%)
Patients with ≥1 TEAE	20 (48.8)	31 (44.3)	26 (59.1)	39 (49.4)
Abasia	4 (9.8)	3 (4.3)	2 (4.5)	5 (6.3)
Fall	3 (7.3)	5 (7.1)	1 (2.3)	5 (6.3)
Back pain	0	3 (4.3)	0	4 (5.1)
Erection increased	1 (2.4)	0	4 (9.1)	0
Pyrexia	1 (2.4)	3 (4.3)	3 (6.8)	0
Vomiting	0	5 (7.1)	1 (2.3)	2 (2.5)

Abbreviations: 0.3/Placebo = patients who received 0.3 mg/kg tadalafil in the OLE and previously received placebo in the double-blind period; 0.3/0.3 = patients who received 0.3 mg/kg tadalafil in both the OLE and double-blind periods; 0.6/Placebo = patients who received 0.6 mg/kg tadalafil in the OLE and previously received placebo in the double-blind period; 0.6/0.6 = patients who received 0.6 mg/kg tadalafil in both the OLE and double-blind periods; MedDRA = Medical Dictionary for Regulatory Activities; N = number of patients in the 6-month I-OLE analysis set; n = number of patients with at least one treatment-emergent adverse event per category; OLE = open-label extension.

[a] Excludes patients from the preferred term count who reported the same treatment-emergent adverse event in both the double-blind and OLE treatment periods.

There were no clinically meaningful effects of tadalafil on laboratory parameters from baseline to endpoint when analysed as mean change or as categorical change (ie, abnormal, low, and high). One patient met criteria for elevated hepatic laboratory results during the 6-month OLE treatment period; however, this patient had elevated total bilirubin since the beginning Of Study LVJJ and throughout the double-blind period due to a preexisting condition of Gilbert's syndrome.

Tadalafil did not have clinically meaningful effects on mean changes or categorical changes from baseline in blood pressure or pulse rate and there were no clinically important findings in ECGs based on mean changes from baseline in quantitative ECG parameters or on the occurrence of treatment-emergent qualitative ECG abnormalities as determined by central evaluation.

4.4. Changes to the Product Information

The following changes to the SmPC are proposed by the MAH:

Section 4.2 – Posology and Method of Administration
As this variation is introducing paediatric data from a DMD population, the following update to the paediatric subsection in Section 4.2 of the SmPC is considered necessary to make it clear that there is no relevant use of Cialis in any paediatric population (i.e., not limited to the treatment of erectile dysfunction).

Cialis SmPC

Paediatric population

There is no relevant use of CIALIS in the paediatric population ~~with regard to the treatment of erectile dysfunction~~.

Correspondingly, the following update is proposed for Section 4.2 of the Adcirca SmPC in order to make it clear that the statement concerning the availability of data in paediatrics refers specifically to the indication of pulmonary arterial hypertension (PAH).

Adcirca SmPC

Paediatric population

The safety and efficacy of ADCIRCA in individuals below 18 years of age has not yet been established. No data are available.

Assessor´s comment

The MAH's proposal for Cialis is not acceptable. The information regarding the use of Cialis in the paediatric population for the approved indication of erectile dysfunction should be maintained.

Therefore, the wording should read as follows:

CIALIS:
Section 4.2, Paediatric population
There is no relevant use of Cialis in the paediatric population with regard to the treatment of erectile dysfunction.

As for Adcirca, section 4.2, Paediatric population should be amended as follows:

ADCIRCA:
The safety and efficacy of Adcirca in ~~individuals below 18 years~~ the paediatric population has not yet been established. ~~No data are available.~~ Currently available data are described in section 5.1.

Section 4.8 – Undesirable effects
The Marketing Authorisation Holder (MAH) is concerned that inclusion of specific text in this section could potentially be confusing and misleading to prescribers and may inadvertently imply that there is evidence that using tadalafil in the paediatric population with DMD could be of some benefit. This is especially so, as the safety profile observed in Study LVJJ was generally consistent with the known safety profile of tadalafil and with adverse events expected in a paediatric DMD population receiving corticosteroids. Thus, inclusion of this reassuring safety data could encourage off-label use and is, therefore, not recommended.

A brief statement on the safety profile from Study LVJJ is proposed for inclusion in Section 5.1, alongside the main description of the study. This allows the information to be communicated to prescribers but the positioning also ensures that the data are seen in context alongside the efficacy results in this population to minimise the potential to encourage or provide justification for off-label use.

Assessor´s comment

The MAH's position is endorsed.

Section 5.1 - Pharmacodynamic properties

Lilly proposes to include a brief summary of the LVJJ study results in this section of the SmPC for Cialis and Adcirca. The summary includes a description of the study population, treatments tested, primary result showing lack of evidence for efficacy, and the safety profile. Lilly considers that these data are sufficient to inform prescribers of the pertinent results from Study LVJJ.

Paediatric population

A randomised, double-blind, placebo-controlled, parallel, 3-arm study of tadalafil was conducted in 331 boys aged 7-14 years with Duchenne muscular dystrophy (DMD) receiving concurrent corticosteroid therapy. The study included a 48-week double blind period where patients were randomised to tadalafil 0.3 mg/kg, tadalafil 0.6 mg/kg, or placebo daily. Tadalafil did not show efficacy in slowing the decline in ambulation as measured by the primary 6 minute walk distance (6MWD) endpoint: least squares (LS) mean change in 6MWD at 48 weeks was -51.0 meters (m) in the placebo group, compared with -64.7 m in the tadalafil 0.3 mg/kg group (p=0.307) and -59.1 m in the tadalafil 0.6 mg/kg group (p=0.538). In addition, there was no evidence of efficacy from any of the secondary analyses performed in this study. The overall safety results from this study were generally consistent with the known safety profile of tadalafil and with adverse events (AEs) expected in a paediatric DMD population receiving corticosteroids.

Assessor´s comment

The MAH's proposal is acceptable with a slightly change. It is considered appropriate to clearly state at the beginning of the paragraph that efficacy was not observed in paediatric patients with DMD. In this sense, an additional sentence is included.
Final wording for section 5.1 should be as follows:

"A single study has been performed in paediatric patients with Duchenne Muscular Dystrophy (DMD) in which no evidence of efficacy was seen. A randomised, double-blind, placebo-controlled, parallel, 3-arm study of tadalafil was conducted in 331 boys aged 7-14 years with DMD receiving concurrent corticosteroid therapy. The study included a 48-week double blind period where patients were randomised to tadalafil 0.3 mg/kg, tadalafil 0.6 mg/kg, or placebo daily. Tadalafil did not show efficacy in slowing the decline in ambulation as measured by the primary 6 minute walk distance (6MWD) endpoint: least squares (LS) mean change in 6MWD at 48 weeks was -51.0 meters (m) in the placebo group, compared with -64.7 m in the tadalafil 0.3 mg/kg group (p=0.307) and -59.1 m in the tadalafil 0.6 mg/kg group (p=0.538). In addition, there was no evidence of efficacy from any of the secondary analyses performed in this study. The overall safety results from this study were generally consistent with the known safety profile of tadalafil and with adverse events (AEs) expected in a paediatric DMD population receiving corticosteroids."

Section 5.2 - Pharmacokinetic properties

As with the consideration to include safety data from Study LVJJ in Section 4.8, the MAH is concerned that inclusion of specific text in this section could potentially be confusing and misleading to prescribers and may inadvertently imply that there is evidence that using tadalafil in the DMD paediatric population could be of some benefit. Given the lack of efficacy of tadalafil in paediatric patients with DMD, Lilly considers that including pharmacokinetic data for tadalafil from a DMD paediatric population would not be useful to prescribers and does not seem warranted. Further, it is unclear how generalisable the pharmacokinetic data for tadalafil in boys 7 – 14 years of age with DMD are to other paediatric populations

Assessor´s comment

The MAH's position is acknowledged.

4.4.1. Discussion

Tadalafil (Cialis, Adcirca) is a selective inhibitor of the phosphodiesterase type 5 (PDE5) enzyme. Tadalafil was approved for the treatment of men with erectile dysfunction (ED) dosed either as needed or once daily and to treat patients with signs and symptoms of benign prostatic hyperplasia (BPH; dosed once daily) under the brand name Cialis. Tadalafil was also approved to treat patients with pulmonary arterial hypertension (PAH, dosed once daily) under the brand name Adcirca.

Tadalafil was considered to have a role in muscle function in DMD. Nonclinical and early clinical studies suggested that relief of microvascular ischemia could reduce use-dependent injury of skeletal muscle, slowing disease progression and slowing the decline in walking ability.

The efficacy and safety of tadalafil as a treatment for ambulatory DMD patients was evaluated in a randomized, double-blind, placebo-controlled, multicentre clinical study with 0.3 mg/kg and 0.6 mg/kg daily dose for 48 weeks. The efficacy outcomes of the study were negative with no effect demonstrated in slowing the decline in ambulation as measured by the primary 6MWD endpoint or any of the secondary endpoints.

Although it was acknowledged that the efficacy or safety results of this study do not impact the benefit-risk assessment for currently approved indications in adults, the CHMP requested a variation to update sections 4.8, 5.1 and 5.2 of the SmPC following their assessment of the Article 46 procedure (EMA/H/C/000436/P46 045 for Cialis and EMEA/H/C/001021/P46 019 for Adcirca) which concluded in August 2016. In this application the MAH has submitted the proposed wording for the Cialis and Adcirca SmPCs. Whereas sections 4.2 and 5.1 have been amended, the MAH is of the opinion that no information should be included in sections 4.8 and 5.2 in order to avoid misleading messages to prescribers and to minimise the potential to encourage or provide justification for off-label use. The CHMP acknowledged that an unjustified off-label use of medicinal products in paediatric population should be avoided.

Input from the SmPC Advisory Group (AG) was requested regarding the most appropriate wording for section 4.2 and whether the MAH's proposal for sections 4.8 and 5.2 (i.e., not to provide any additional information) was acceptable in the view of the group. After discussion, the MAH was requested to implement the changes as above indicated which has been done by the MAH.

5. Request for supplementary information

5.1. Major objections

None

5.2. Other concerns

SmPC wording

1. The MAH is requested to implement the changes in section 4.2 and section 5.1 as indicated in this report.

6. Assessment of the responses to the request for supplementary information

SmPC wording

1. The MAH is requested to implement the changes in section 4.2 and section 5.1 as indicated in this report.

MAH position

All of the requests in the assessment report have been implemented in the product information. In addition to the changes requested in the RSI, the opportunity has also been taken to introduce changes to Annex II from the latest QRD template. This change is tracked in the tracked changes version of the product information supplied in the working documents.

Assessor´s comment

The MAH has implemented the requested changes in sections 4.2 and 5.1 of both SmPCs. Final texts presented for the Cialis and Adcirca SmPCs are in line with the comments made and therefore, acceptable.

Regarding the additional change implemented in Annex II, this is endorsed.

Please refer to the Product Information for Adcirca and Cialis that are circulated with this report.