Continuation and effectiveness of tadalafil once daily during a 6-month observational study in erectile dysfunction: the EDATE study

J. Buvat,1 D. Hatzichristou,2 F. G. Boess,3 H. Büttner,4 N. Gehchan,5 C. Henneges,6 H. Porst2

Introduction

The efficacy and safety of oral phosphodiesterase type 5 (PDE5) inhibitors such as sildenafil citrate (sildenafil), tadalafil and vardenafil HCl (vardenafil) for treatment of erectile dysfunction (ED) – have been well-documented in randomised, placebo-controlled studies (1–5) and systematic meta-analyses (6,7). However, high treatment discontinuation rates of 50–60% have been reported for short-acting PDE5-inhibitors used on-demand (pro re nata, PRN) in naturalistic settings (8). Men starting PDE5-inhibitors face multiple obstacles that may lead to early dissatisfaction and subsequent treatment discontinuation (8). One major factor affecting effectiveness of PDE5-inhibitors in clinical practice is inadequate patient instruction during the initial prescription process. Hatzichristou and coworkers have found that the response rate to sildenafil may be maximised after appropriate dose-titration and instruction on administration (9). A potential restraint of short-acting PDE5-inhibitors is the required temporal association between drug intake and timing of sexual intercourse. In contrast to the short-acting PDE5-inhibitors sildenafil or vardenafil, tadalafil has a long half-life (17.5 h) and has been shown to improve erectile function (EF) up to 36 h postdose (PRN administration) (10,11).

The greater flexibility and uncoupling of drug intake and sexual activity leads to improvements in time concerns, sexual self-confidence and spontaneity (12,13).
investigator for trials sponsored by Eli Lilly, Bayer-Scherling, Boehringer Ingelheim, and Janssen-Cilag. FB, HB, NG and CH are employees of Eli Lilly and Company; HB, NG and FB also own Lilly stock. HP has received honoraria as consultant for Eli Lilly, Bayer Healthcare and Menarini/Berlin-Chemie, and he has been a clinical trial investigator for trials sponsored by these companies. DH has been an Advisory Board Member for Eli Lilly and Menarini, has received speaker honoraria from Bayer, Menarini and Eli Lilly, and has been a clinical trial investigator for studies sponsored by Eli Lilly and Pfizer.

The long half-life of tadalafil allowed the development of a once daily (OaD) dosing strategy (4,14). The resulting OaD regimen (tadalafil 5 mg/day) was well-tolerated and significantly improved ED in randomised controlled trials (RCTs) (4,5,15,16). Furthermore, the OaD regimen improved the sexual quality of life of couples to a level comparable to that experienced prior to onset of ED in controlled studies (17,18).

However, no prospective data on the use of tadalafil OaD treatment in routine practice, and no information on continuation rates of patients treated with tadalafil OaD in naturalistic settings are available so far. This observational study in men with ED, with or without previous exposure to PDE5-inhibitors, assessed their reasons for choosing or switching to different PDE5-inhibitors, documented effectiveness and tolerability of tadalafil 5 mg OaD under routine conditions and observed as primary outcome the time to treatment switch or discontinuation in those men initiating tadalafil 5 mg OaD at baseline.

Methods

Patients and Study Design

This prospective, multicenter, longitudinal, naturalistic observational study (H6D-EW-LVIU) was conducted in Germany, France, Italy and Greece. Centres were invited sequentially from a randomised list of 205 candidate centres that had expressed interest in participation; 97 centres signed the contract, 59 actually enrolled patients. Patients were consecutively enrolled between November 2011 and June 2012. Adult male patients who met the criteria for ED according to the investigator and presented within the normal course of care were eligible to participate in the study, if they had decided together with their physician to either initiate PDE5-inhibitor treatment for the first time (treatment-naïve) or to switch from any previous PDE5-inhibitor. Patients who had previously used tadalafil OaD were excluded. The observational nature of the study was confirmed by the appropriate ethical review boards in each participating country and patients provided written informed consent to data collection, storage and release of anonymised data.

Assessment and treatment of patients was based solely on the investigator’s routine practice in the provision of care to ED patients.

At baseline (T1), data were collected for all patients (overall cohort). At two postbaseline observational time points (T2, T3), data were collected only for those patients who initiated or switched to tadalafil OaD at baseline (tadalafil OaD cohort). T2 and T3 data were collected at routine visits within 1–3 months and 4–6 months only for patients switching to or starting tadalafil OaD treatment. Patients who initiated or switched to tadalafil OaD at baseline but switched or discontinued this treatment during the observation were followed up until the end of the 6-month observation period. A telephone follow-up call was performed if a patient had no visit within 4–6 months after baseline.

Outcome measures

The primary objective was to assess the time to treatment discontinuation of tadalafil OaD in men who had initiated or switched to tadalafil OaD at baseline (i.e. in the tadalafil OaD cohort). Time to discontinuation was measured as the number of days from start of tadalafil OaD treatment until switch to any other PDE5-inhibitor PRN or discontinuation of any PDE5-inhibitor treatment. Treatment breaks ≤ 6 weeks without switch to a different ED medication were not considered as discontinuation of tadalafil OaD. Patients lost to follow-up and without response to telephone follow-up were censored at the date of the last contact.

Secondary outcomes based on the data collected for the overall cohort include patient characteristics and reasons for the choice/switch of PDE5 inhibitor treatment at baseline. Secondary outcomes based on the longitudinal observation of the tadalafil OaD cohort include treatment switching patterns and reasons for switches or discontinuations, and the following EF assessments: (i) International Index of Erectile Dysfunction – Erectile Function (IIEF-EF) domain score (19,20), (ii) percent ‘yes’ responses to Global Assessment Questions (GAQ-1: ‘Has the treatment you have been taking during this study improved your erections?’; GAQ-2: ‘Has the treatment improved your ability to engage in sexual activity?’).

Safety was evaluated by assessing treatment-emergent adverse events (TEAEs) reported during tadalafil OaD treatment (Medical Dictionary for Regulatory Activities; MedDRA version 15.0).

Statistical analysis

Sample size

Assuming that 50–80% of patients who initiated tadalafil OaD at baseline would continue on tadalafil OaD until Month 6 (21), a sample size of 200 patients in the tadalafil OaD cohort would allow an estimation of the continuation rate and the associated 95% confidence interval (CI) with an appropriate precision ranging between ± 5.5% and ± 6.9%. Accounting for 20% loss to follow-up (21), it was...
planned to enrol 250 patients initiating tadalafl OaD at baseline. Assuming that 10% of all patients enrolled would initiate tadalafl OaD at baseline, then for 250 tadalafl OaD patients to be enrolled into the 6-month observation period, a total of 2500 baseline data collection forms for patients initiating/switching to any PDE5-inhibitor would be needed. Assuming a questionnaire response rate of 85%, placement of 3000 questionnaires was required for a return of 2500 completed baseline data collection forms. Therefore, consecutive enrolment was planned to be stopped as soon as either 3000 patients were enrolled overall, or 600 patients were enrolled into the tadalafl OaD cohort.

Primary analysis
All patients prescribed tadalafl OaD treatment at baseline were included in the analysis. The distribution of time to discontinuation of tadalafl OaD was estimated using the Kaplan–Meier product-limit method. The Kaplan–Meier proportions and associated 95% CIs of patients on tadalafl OaD at 2, 4 and 6 months were reported. An additional exploratory analysis investigated the association between time to discontinuation of tadalafl OaD and selected baseline factors using a Cox proportional hazards model; hazard ratios (HR) and the corresponding 95% CIs are reported. The final model was developed as follows: factors associated with treatment discontinuation were identified using backward selection (removed if p > 0.1). These factors were then reviewed to define a final model. The final model included baseline factors for presence or absence of relevant comorbidities, type of physician who initially diagnosed the ED, country, duration of living arrangement, age, ED aetiology, ED severity and work status. Additional sensitivity analyses were conducted to check if the goodness of fit based on the Akaike Information Criterion (AIC) could be improved by exchanging or deleting variables from the model (22). Also, these analyses were complemented by corresponding logistic regression analyses to investigate the association between continuation of tadalafl OaD treatment at T3, following the same procedure as for the Cox proportional hazards model except using forward selection (included if p ≤ 0.1).

Secondary analyses
All patients who provided consent to release information and fulfilled the study entry criteria were included in the cross-sectional baseline data analysis. All patients prescribed tadalafl OaD at baseline were included in the longitudinal analyses. Reasons for initiating or switching to different PDE5-inhibitors at T1 were assessed descriptively. Logistic regression models were developed to investigate factors potentially associated with the initial choice of or switch to tadalafl OaD at baseline; odds ratios (ORs) and 95% CIs are reported. Factors associated with the choice of or switch to tadalafl OaD were initially identified using forward selection (included if p ≤ 0.1), and then reviewed to define the final model. The final model for the initial choice of tadalafl OaD included the factors body mass index (BMI), decreased duration of erection compared with pre-ED status, prior pelvic surgery, ED severity, duration of living arrangement, country, presence vs. absence of concomitant antihypertensive treatment, presence vs. absence of concomitant insulin treatment, type of physician who diagnosed the ED and education status. The final model investigating switches to tadalafl OaD included the factors age, country, ED aetiology, decreased libido compared with pre-ED status, ED severity, duration of living arrangement and work status.

Changes in IIEF-EF domain scores were assessed using a mixed model for repeated measures, including the following prespecified covariates as fixed effects: age (18–65 vs. > 65 years), benign prostate hyperplasia (BPH) (yes vs. no), cardiovascular disease (yes vs. no), country, diabetes (yes vs. no), dyslipidaemia (yes vs. no), aetiology of ED, pretreatment with PDE5-inhibitors (yes vs. no), ED severity and visit. A corresponding model was calculated including only those patients who remained on tadalafl OaD throughout the observation. GAQ- and safety data were evaluated descriptively.

In case of missing data, the number of patients with data available is given in the figures/tables. For Cox proportional hazards and logistic regression models, patients with missing data had to be excluded from the specific model(s) that needed the missing variables. Data were analysed using the SAS 9.2 software (SAS Institute Inc., Cary, NC).

Results
Patient characteristics (overall cohort)
Overall, 975 men with ED who decided together with their physician to initiate or switch to a new PDE5-inhibitor treatment were enrolled and had baseline documentation (Germany 401, France 269, Italy 166, Greece 139). The majority (778, 79.8%) received prescriptions for initiation or switch to tadalafl OaD at baseline; the remaining 197 (20.2%) were prescribed PDE5-inhibitors PRN; mainly tadalafl PRN (135, 13.9%) and less frequently vardenafil (33, 3.4%) or sildenafil (29, 3.0%). The distribution of age and other demographical data in the tadalafl OaD and tadalafl, vardenafil and sildenafil PRN cohorts are
shown in Table 1. Mean (SD) IIEF-EF baseline scores were 14.5 (7.06) in the tadalafil OaD and 17.0 (6.25) in the tadalafil PRN cohort.

Overall, 33.7% of all men enrolled reported that they had previously used PDE5-inhibitors PRN at any time prior to baseline (tadalafil OaD cohort: 34.3%); 24.6% reported any pharmacological ED treatment within the last 3 months (tadalafil OaD cohort: 23.5%), mainly PDE5-inhibitors PRN (Table 1).

Cardiovascular disorders, hypertension, dyslipidemia and diabetes were the most frequent relevant comorbidities (Table 1; Supplementary Tables S1 and S2 present the underlying preferred terms). In the tadalafil OaD cohort, 11.4% of 778 patients reported any previous pelvic surgery.

Reasons for choice of PDE5-inhibitor (overall cohort)
The reported reasons for choosing the specific PDE5-inhibitor treatment initiated or switched to at baseline are shown in Table 2. In PDE5-inhibitor naïve patients, clinical experience of the investigator and patient preference were the most frequent reasons for initiation (tadalafil OaD cohort: clinical experience 52.3%, patient preference 22.4%). For patients treated previously with PDE5-inhibitors, reasons for switching varied depending on the cohort. For patients switching to tadalafil OaD, lack of efficacy of previous treatment (25.3%/11.4%), preference for OaD treatment (25.3%), the feeling that their previous medication controlled their sexual life (8.9%) and partner request (8.9%) were the most frequent reasons to switch.

Supplementary Figures S1 and S2 summarise the logistic regression analyses investigating the baseline factors potentially associated with the initial choice and switch to tadalafil OaD, respectively. Duration of the patients’ living arrangement was significantly associated with both initial choice and switch to tadalafil OaD. Patients with longer duration were less likely to start with (p = 0.044) or switch to (p = 0.006) tadalafil OaD at baseline. Patients with higher BMI (p = 0.008), prior pelvic surgery (p = 0.047), or concomitant insulin treatment (p = 0.012) were less likely to start their initial ED treatment with tadalafil OaD. Patients with both

| Table 1 Patient characteristics                                      | TAD OaD | TAD PRN | VAR PRN | SIL PRN | Overall |
|---------------------------------------------------------------------|--------|--------|--------|--------|---------|
| **Age, years**                                                      |        |        |        |        |         |
| Median (IQR)                                                        | 57 (47–65) | 57 (46–65) | 57 (52–66) | 70 (54–73) | 57 (47–65) |
| > 65 years, n (%)                                                   | 180 (23.1) | 30 (22.2) | 10 (30.3) | 15 (51.7) | 235 (24.1) |
| **Origin, n (%)**                                                   |        |        |        |        |         |
| Caucasian                                                           | 523 (67.2) | 119 (88.1) | 30 (90.9) | 28 (96.6) | 700 (71.8) |
| Other*                                                              | 4 (0.5) | 2 (1.5) | 0 | 0 | 6 (0.6) |
| Missing data†                                                       | 251 (32.3) | 14 (10.4) | 3 (9.1) | 1 (3.4) | 269 (27.6) |
| **Education level, n (%)**                                          |        |        |        |        |         |
| N with data                                                         | 776 | 135 | 32 | 29 | 972 |
| No formal education                                                 | 11 (1.4) | 0 (0.0) | 2 (6.3) | 1 (3.4) | 14 (1.4) |
| Primary school                                                      | 203 (26.2) | 37 (27.4) | 11 (34.4) | 5 (17.2) | 256 (26.3) |
| Secondary school                                                    | 328 (42.3) | 62 (45.9) | 11 (34.4) | 14 (48.3) | 415 (42.7) |
| University/post graduate                                            | 228 (29.4) | 29 (21.5) | 7 (21.9) | 6 (20.7) | 270 (27.8) |
| Unknown                                                             | 6 (0.8) | 7 (5.2) | 1 (3.1) | 3 (10.3) | 17 (1.7) |
| **Work status, n (%)**                                              |        |        |        |        |         |
| N with data                                                         | 776 | 135 | 33 | 29 | 973 |
| Full-time                                                           | 433 (55.8) | 78 (57.8) | 10 (30.3) | 11 (37.9) | 532 (54.7) |
| Part-time                                                           | 31 (4.0) | 5 (3.7) | 5 (15.2) | 1 (3.4) | 42 (4.3) |
| Pensioner/retired                                                   | 266 (34.3) | 46 (34.1) | 12 (36.4) | 17 (58.6) | 341 (35.0) |
| Student                                                             | 10 (1.3) | 0 | 2 (6.1) | 0 | 12 (1.2) |
| Unemployed/unable to work                                           | 32 (4.1) | 5 (3.7) | 4 (12.1) | 0 | 41 (4.2) |
| Other                                                               | 4 (0.5) | 1 (0.7) | 0 | 0 | 5 (0.5) |
| **Marital status, n (%)**                                           |        |        |        |        |         |
| N with data                                                         | 776 | 135 | 31 | 28 | 970 |
| Married                                                             | 494 (63.7) | 103 (76.3) | 18 (58.1) | 24 (85.7) | 639 (65.9) |
| Partnered, living together                                          | 96 (12.4) | 13 (9.6) | 9 (29.0) | 2 (7.1) | 120 (12.4) |
| Table 1 Continued                                                                 |
|----------------------------------------------------------------------------------|
|                                                                                 |
| | TAD OaD | TAD PRN | VAR PRN | SIL PRN | Overall |
| | N = 778 | N = 135 | N = 33  | N = 29  | N = 975  |
| Partnered, living separately                                                   | 89 (11.5) | 8 (5.9) | 1 (3.2) | 1 (3.6) | 99 (10.2) |
| No relationship                                                                 | 11 (1.4)  | 1 (0.7) | 1 (3.2) | 0       | 13 (1.3)  |
| Other†                                                                         | 86 (11.1) | 10 (7.4) | 2 (6.5) | 1 (3.6) | 99 (10.2) |
| **Duration of living arrangement, years**                                       |           |          |         |          |          |
| Median (IQR)                                                                   | 17 (4–31) | 21 (10–30) | 15 (6–32) | 29 (11–43) | 18 (5–31) |
| **IIEF-EF at baseline**                                                          |           |          |         |          |          |
| Mean (SD)                                                                      | 14.5 (7.06) | 17.0 (6.25) | 12.9 (6.39) | 14.7 (6.55) | 14.8 (6.97) |
| **ED severity (investigator assessment), n (%)**                                |           |          |         |          |          |
| N with data                                                                     | 775       | 135      | 31      | 27      | 968      |
| Mild                                                                            | 160 (20.6) | 31 (23.0) | 4 (12.9) | 4 (14.8) | 199 (20.6) |
| Moderate                                                                       | 411 (53.0) | 79 (58.5) | 14 (45.2) | 14 (51.9) | 518 (53.5) |
| Severe                                                                          | 204 (26.3) | 25 (18.5) | 13 (41.9) | 9 (33.3) | 251 (25.9) |
| **Duration of ED symptoms, n (%)**                                              |           |          |         |          |          |
| N with data                                                                     | 776       | 135      | 31      | 27      | 969      |
| < 3 months                                                                      | 55 (7.1)  | 12 (8.9) | 3 (9.7) | 2 (7.4) | 72 (7.4)  |
| 3 to < 12 months                                                                | 231 (29.7) | 28 (20.7) | 8 (25.8) | 9 (33.3) | 276 (28.3) |
| ≥ 12 months                                                                     | 490 (63.1) | 95 (70.4) | 20 (64.5) | 16 (59.3) | 621 (64.1) |
| **ED aetiology, n (%)**                                                         |           |          |         |          |          |
| N with data                                                                     | 776       | 135      | 31      | 27      | 969      |
| Mixed                                                                           | 343 (44.2) | 80 (59.3) | 8 (25.8) | 12 (44.4) | 443 (45.7) |
| Organic                                                                         | 240 (30.9) | 26 (19.3) | 14 (45.2) | 6 (22.2) | 286 (29.5) |
| Psychogenic                                                                     | 145 (18.7) | 20 (14.8) | 4 (12.9) | 3 (11.1) | 172 (17.8) |
| Unknown                                                                         | 48 (6.2)  | 9 (6.7)  | 5 (16.1) | 6 (22.2) | 68 (7.0)  |
| **Penile defects, n (%)**                                                       |           |          |         |          |          |
| N with data                                                                     | 310       | 45       | 30       | 12       | 376       |
| Libido decreased                                                                | 183 (23.5) | 40 (29.6) | 5 (15.2) | 12 (41.4) | 240 (24.6) |
| Sildenafil                                                                      | 59 (7.6)  | 24 (17.8) | 2 (6.1)  | 2 (6.9)  | 87 (8.9)  |
| Tadalafil PRN                                                                   | 63 (8.1)  | 1 (0.7)  | 3 (9.1)  | 6 (20.7) | 73 (7.5)  |
| Vardenafil                                                                      | 52 (6.7)  | 12 (8.9) | 0        | 3 (10.3) | 67 (6.9)  |
| Prostaglandines                                                                 | 13 (1.7)  | 0        | 0        | 0        | 13 (1.3)  |
| Yohimbine                                                                        | 2 (0.3)   | 2 (1.5)  | 0        | 0        | 4 (0.4)   |
| **Relevant categories of comorbidities, n (%)**                                  |           |          |         |          |          |
| N with data                                                                     | 268       | 46       | 13       | 7        | 334       |
| Cardiovascular disorder                                                         | 260 (33.4) | 46 (34.1) | 13 (39.4) | 7 (24.1) | 326 (33.4) |
| Hypertension                                                                    | 144 (18.5) | 19 (14.1) | 8 (24.2) | 6 (20.7) | 177 (18.2) |
| Diabetes                                                                        | 124 (15.9) | 27 (20.0) | 10 (30.3) | 3 (10.3) | 164 (16.8) |
| Pelvic surgery                                                                  | 89 (11.4) | 12 (8.9) | 7 (21.2) | 3 (10.3) | 111 (11.4) |
| BPH                                                                              | 49 (6.3)  | 7 (5.2)  | 1 (3.0)  | 4 (13.8) | 61 (6.3)  |
| Hypogonadism                                                                    | 12 (1.5)  | 0        | 2 (6.1)  | 0        | 14 (1.4)  |

*Other includes: Asian (3), Black or African American (2), multiple (1). †Because of legal restrictions in France, patient origin was not included on the electronic case report forms for patients from France. ‡Other includes: divorced, legally separated, married but living separate, never married, widowed. §Other includes: testosterone, Nebido, Androtardyl, papaverine, phentolamine. BPH, benign prostate hyperplasia; ED, erectile dysfunction; IIEF-EF, International Index of Erectile Function, erectile function [EF] domain score; IQR, interquartile range; N, number of patients with data; n, number of patients; OaD, once a day; PRN, pro re nata, i.e. on-demand; SD, standard deviation; SIL, sildenafil; TAD, tadalafil; VAR, vardenafil.
Table 2 Reasons for choice of the PDE5-inhibitor initiated or switched to at baseline

|                                      | Number (% of patients) | Initiated treatment (PDE5-I naive) | Switched treatment (PDE5-I pretreated) | Overall  |
|--------------------------------------|-------------------------|-------------------------------------|----------------------------------------|----------|
|                                      |                         | 497 (100.0)                         | 79 (100.0)                             | 576 (100.0) |
| Tadalafil OaD cohort (N = 778)       |                         |                                    |                                        |          |
| N with data                          |                         | 260 (52.3)                          | 0                                       | 260 (45.1) |
| Clinical experience                  |                         | 129 (26.0)                          | 0                                       | 129 (22.4) |
| Patient preference                   |                         | 21 (4.2)                            | 0                                       | 21 (3.6)  |
| Lack of efficacy (hardness of erection) |                     | 0                                   | 20 (25.3)                              | 20 (3.5)  |
| Preference for OaD treatment         |                         | 0                                   | 20 (25.3)                              | 20 (3.5)  |
| Patient experience                   |                         | 18 (3.6)                            | 0                                       | 18 (3.1)  |
| Tolerability                         |                         | 12 (2.4)                            | 0                                       | 12 (2.1)  |
| Lack of efficacy (duration of erection) |                     | 0                                   | 9 (11.4)                               | 9 (1.6)   |
| Felt that medication controls his sexual life |                 | 0                                   | 7 (8.9)                                | 7 (1.2)   |
| Partner’s request                    |                         | 0                                   | 7 (8.9)                                | 7 (1.2)   |
| Co-treatment of comorbidities        |                         | 35 (38.9)                           | 0                                       | 35 (36.8) |
| Lack of confidence medication would work |                 | 30 (33.3)                           | 0                                       | 30 (31.6) |
| Lack of efficacy                     |                         | 1 (5.6)                             | 0                                       | 1 (5.3)   |
| Low costs                            |                         | 4 (4.4)                             | 0                                       | 4 (4.2)   |
| Product labelling                    |                         | 3 (3.3)                             | 0                                       | 3 (3.2)   |
| Tolerability                         |                         | 4 (10.5)                            | 0                                       | 4 (13.7)  |
| Other†                               |                         | 11 (39.3)                           | 0                                       | 11 (39.3) |
| Adverse events                       |                         | 9 (32.1)                            | 0                                       | 9 (32.1)  |
| Other†                               |                         | 4 (14.3)                            | 0                                       | 4 (14.3)  |
| Co-treatment of comorbidities        |                         | 3 (10.7)                            | 0                                       | 3 (10.7)  |
| Product labelling                    |                         | 1 (3.6)                             | 0                                       | 1 (3.6)   |
| Vardenafil PRN cohort (N = 33)       |                         | 28 (100.0)                          | 0                                       | 28 (100.0) |
| N with data                          |                         | 11 (39.3)                           | 0                                       | 11 (39.3) |
| Patient preference                   |                         | 9 (32.1)                            | 0                                       | 9 (32.1)  |
| Clinical experience                  |                         | 4 (14.3)                            | 0                                       | 4 (14.3)  |
| Low costs                            |                         | 3 (10.7)                            | 0                                       | 3 (10.7)  |
| Product labelling                    |                         | 1 (3.6)                             | 0                                       | 1 (3.6)   |
| Sildenafil PRN cohort (N = 29)        |                         | 14 (100.0)                          | 3 (100.0)                              | 17 (100.0) |
| N with data                          |                         | 7 (50.0)                            | 0                                       | 7 (41.2)  |
| Clinical experience                  |                         | 4 (28.6)                            | 0                                       | 4 (23.5)  |
| Tolerability                         |                         | 3 (21.4)                            | 0                                       | 3 (17.6)  |
| Lack of efficacy (duration of erection) |                 | 0                                   | 1 (33.3)                               | 1 (5.9)   |
| Lack of efficacy (hardness of erection) |                 | 0                                   | 1 (33.3)                               | 1 (5.9)   |
| Slow onset of action                 |                         | 0                                   | 1 (33.3)                               | 1 (5.9)   |

*For tadalafil OaD, ‘other’ includes: adverse event, allergy to alternate therapy, cost of medication, no contraindication for comorbidity, non-desired spontaneous erections, patient discontinuation from trial, time constraints because of short window of drug action, other (not specified).
†For tadalafil PRN, ‘other’ includes: preference for PRN treatment, patient experience, insurance reasons, lack of efficacy (hardness of erection), no/few drug interactions, time constraints because of short window of drug, other (not specified).

N, number of patients; OaD, once a day; PDE5-I, phosphodiesterase type 5 inhibitor; PRN, pro re nata; i.e. on-demand.
severe and mild ED were more likely to switch to tadalafil OaD than patients with moderate ED \( (p = 0.001 \text{ and } p = 0.026, \text{ respectively}) \).

**Patient disposition (tadalafil OaD cohort)**

Overall, 778 men received a prescription for initiation or switch to tadalafil OaD at baseline and were included in the longitudinal part of the study, 643 (82.7%) completed the observation. Of the 778 men in the tadalafil OaD cohort, 510 (65.6%) were prescribed tadalafil OaD as their first PDE5-inhibitor (PDE5-inhibitor naïve) and 267 (34.3%) had been treated previously with other PDE5-inhibitors (one patient had missing data). Figure 1 summarises patient disposition and treatment patterns during the 6-month for the overall tadalafil OaD cohort (Table 3 presents corresponding data for treatment-naïve and previously treated patients). Of those 643 patients who completed the study, the majority remained on tadalafil OaD treatment until the end of observation, i.e. 94.8% of treatment-naïve patients and 94.6% of patients treated previously with PDE-inhibitors PRN. Overall, 91.0% of all 643 study completers reported they would continue on tadalafil OaD, regardless if they were treatment-naïve or treated previously with any PRN treatment. Only 4.7% of all study completers switched directly to a PRN treatment during or at the end of the study (PDE5-inhibitor naïve 4.3% of 420, PDE5-inhibitor pretreated 5.4% of 223 patients). A total of 135 patients stopped their participation in the study prior to completion of the 6-month observation period. Of these 135 patients, 75 (55.6%) reported they would continue to take tadalafil OaD; 6.7% switched directly to a PRN regimen during the study or at discontinuation (PDE5-inhibitor naïve 5.5% of 90, PDE5-inhibitor pretreated 11.6% of 44 patients).

**Time to discontinuation of tadalafil OaD (primary outcome)**

Excluding five patients who were prescribed tadalafil OaD at baseline but did not take it, 773 patients provided data for Kaplan–Meier analysis. Of these, 107 had discontinuation events during the 6-month

| Table 3 | Treatment patterns of patients initiating or switching to tadalafil OaD at baseline |
|---------|----------------------------------------------------------------------------------|
|         | Number (%) of patients                                                           |
|         | PDE5-I naïve                      | PDE5-I pretreated                     | Overall     |
|         | \( N = 510 \)                      | \( N = 267 \)                         | \( N = 778^* \) |
| **Completed observation** | | | |
| No switch, continued tadalafil OaD after completion† | 420 (82.1) | 223 (83.6) | 643 (82.7) |
| No switch, stopped tadalafil OaD at completion | 382 (74.9) | 203 (75.6) | 585 (75.7) |
| No switch, treatment break | 13 (2.5) | 6 (2.3) | 19 (2.5) |
| Switched from tadalafil OaD to | | | |
| Tadalafil PRN‡ | 8 (1.6) | 5 (1.9) | 13 (1.7) |
| Vardenafil PRN | 6 (1.2) | 5 (1.9) | 11 (1.4) |
| Sildenafil PRN | 4 (0.8) | 2 (0.8) | 6 (0.8) |
| Other | 2 (0.4) | 0 (0.0) | 2 (0.3) |
| **Added treatments to tadalafil OaD** | | | |
| Vardenafil PRN and tadalafil PRN | 1 (0.2) | 0 (0.0) | 1 (0.1) |
| Other (testosterone) | 0 (0.0) | 1 (0.4) | 1 (0.1) |
| Tadalafil OaD prescribed but not taken | 2 (0.4) | 0 (0.0) | 2 (0.3) |
| **Discontinued observation** | | | |
| No switch, continued tadalafil OaD after discontinuation§ | 90 (100.0) | 44 (100.0) | 135 (100.0) |
| No switch, stopped tadalafil OaD at discontinuation | 50 (55.6) | 24 (54.5) | 74 (54.5) |
| Switched from tadalafil OaD to | | | |
| Tadalafil PRN | 0 (0.0) | 4 (9.1) | 4 (3.0) |
| Vardenafil PRN§ | 4 (4.4) | 1 (2.3) | 5 (3.7) |
| Tadalafil OaD prescribed but not taken | 1 (1.1) | 2 (4.5) | 3 (2.2) |

*For 1 patient, previous PDE5-I treatment status was unknown. †Includes one patient who received TAD-OaD at a higher dose of 10 mg OaD for 1 month. ‡Includes one patient who was censored because he used tadalafil PRN during a treatment break. §Includes one patient who additionally switched from tadalafil 5 mg OaD to tadalafil 5 mg every other day. N, number of patients; OaD, once a day; PDE5-I, phosphodiesterase type 5 inhibitor; PRN, pro re nata, i.e. on-demand.
Total enrolled
\[ n = 975 \]

Initiated/switched to PDE5-inhibitor PRN:
- T1 documentation only
  - Tadalafil PRN 135
  - Vardenafil PRN 33
  - Sildenafil PRN 29

Initiated/switched to tadalafil OaD:
- Started longitudinal observation
  \[ n = 778 \] (100.0%)

Discontinued observation\(^a\)
\[ n = 135 \] (17.4%)
- No switch, continued tadalafil OaD after study discontinuation 75 (9.6%)
- No switch, stopped tadalafil OaD at study discontinuation 48 (6.2%)
- Switched to PDE5-inhibitor PRN before study discontinuation 9 (1.2%)
- Tadalafil OaD prescribed but not taken 3 (0.4%)

Completed observation\(^b\)
\[ n = 643 \] (82.6%)
- No switch, continued tadalafil OaD after study 585 (75.2%)
- No switch, stopped tadalafil OaD at end of study 19 (2.4%)
- Switched to PDE5-inhibitor PRN during study 30 (3.9%)
- Other treatment changes 4 (0.5%)
- No switch, but treatment break during study 3 (0.4%)
- Tadalafil OaD prescribed but not taken 2 (0.3%)

Figure 1 Patient disposition. \( N \), number of patients; OaD, once a day; PRN, pro re nata, i.e. on-demand; T1, baseline, T2, T3, postbaseline observations. \(^a\)Patients discontinued from the observation may have stayed on tadalafil OaD, or may have discontinued tadalafil OaD at any time. Reasons for discontinuation of the observation included: patient decision 51 (6.6%), lost to follow-up 38 (4.9%), lack of efficacy 28 (3.6%), adverse event 15 (1.9%), physician decision 3 (0.4%).

\(^b\)Completers were defined as patients who had a full record of T1, T2 and T3 documentations, and may or may not have discontinued tadalafil OaD during the observation.

observation (defined as documented end date of tadalafil OaD treatment, irrespective if the patient completed or discontinued the study). 94.0% (95% CI: 92.3, 95.7), 88.3% (85.9, 90.6) and 86.3% (83.7, 88.9) of patients still adhered to tadalafil OaD at 2, 4 and 6 months, respectively (Kaplan–Meier estimates). Therefore, the median for time to discontinuation of tadalafil OaD could not be estimated (Figure 2). The 25th percentile of time to switch/discontinuation of tadalafil OaD was estimated as 31.1 weeks (lower 95% CI 30.3 weeks). Three patients reported one or two treatment breaks ranging from 7 to 14 days, these were not considered as discontinuation events.

**Reasons for discontinuation of tadalafil OaD**

Among the 107 patients with documented discontinuation of tadalafil OaD treatment (13.8% of all 778), the most frequent reason for discontinuation was lack of efficacy (hardness of erection), both for PDE5-inhibitor naïve and pretreated patients (25.4% of 71 and 41.7% of 36 discontinued patients, respectively; Table 4). Other common reasons were adverse

Figure 2 Kaplan–Meier estimation for time to discontinuation of tadalafil OaD treatment. CI, confidence interval; NE, not estimable; OaD, once a day.
event (22.5% and 16.7%), cost of medication (16.1% and 11.1%) and reluctance to take a pill every day (9.9% and 13.9%).

Figure 3 summarises results of the Cox proportional hazard model investigating baseline factors potentially associated with time to discontinuation of Tadalafil OaD treatment (Cox proportional hazards model; 734 patients included in model). Model goodness of fit (AIC): 1267.347. AIC, akaike information criterion; CI, confidence interval; ED, erectile dysfunction; HR, hazard ratio; OaD, once a day; PDE5-I, phosphodiesterase type 5 inhibitor; TAD, tadalafil.

Table 4  Reasons for discontinuation of tadalafil OaD treatment

| Reasons                                      | Number (%) of patients |
|----------------------------------------------|------------------------|
| Discontinued TAD-OaD†                        |                        |
| Lack of efficacy (hardness of erection)      | 18 (25.4) 15 (41.7) 33 (30.8) |
| Adverse event                                | 16 (22.5) 6 (16.7) 22 (20.6) |
| Cost of medication                           | 12 (16.9) 4 (11.1) 16 (15.0) |
| Did not want to take a pill every day         | 7 (9.9) 5 (13.9) 12 (11.2) |
| Patient discontinued study                   | 8 (11.3) 1 (2.8) 9 (8.4) |
| Partner’s request                            | 3 (4.2) 2 (5.6) 5 (4.7) |
| Felt that medication controlled his sexual life | 3 (4.2) 0 3 (2.8) |
| Slow onset of action                         | 3 (4.2) 0 3 (2.8) |
| Lack of efficacy (duration of erection)      | 0 2 (5.6) 2 (1.9) |
| Lack of confidence in medication             | 0 1 (2.8) 1 (0.9) |
| Non-desired spontaneous erections            | 1 (1.4) 0 1 (0.9) |

*For one patient, previous PDE5-I treatment status was unknown. †Includes all patients with documented end date of tadalafil OaD treatment, irrespective if the patient completed or discontinued the study. N, number of patients; OaD, once a day; PDE5-I, phosphodiesterase type 5 inhibitor; TAD, tadalafil.

© 2014 The Authors. International Journal of Clinical Practice Published by John Wiley & Sons Ltd.

Int J Clin Pract, September 2014, 68, 9, 1087–1099

Tadalafil OaD continuation and effectiveness 1095
tadalafil OaD. Initial ED diagnosis by a general practitioner was associated with a decreased risk for treatment discontinuation vs. initial diagnosis by an urologist (p < 0.001). Longer duration of living arrangement was associated with an increased risk for treatment discontinuation (p = 0.019), as was older age (p = 0.038). In the complementary logistic regression analysis investigating factors associated with continuation of tadalafil at T3, duration of living arrangement (p = 0.034), but not age, was significantly associated with treatment continuation (Figure S3).

Erectile function (IIEF-EF, GAQ)
For the overall tadalafil OaD cohort, least-square mean (LS mean) (95% CI) IIEF-EF domain scores increased statistically significantly by 6.2 (4.8, 7.5) points from baseline to T2 and by 7.1 (5.8, 8.5) points from baseline to the final observation (p < 0.001 for both). Considering only those patients who stayed on tadalafil OaD throughout the observation, increases were 6.0 (4.7, 7.4) points from baseline to T2 and 6.9 (5.6, 8.3) points to the final observation (p < 0.001 for both).

At the final observation, 91.1% of patients reported that treatment had improved their erection (GAQ-1; 88.4% at T2), and 86.1% reported that treatment had improved their ability to engage in sexual activity (GAQ-2; 81.9% at T2). Final observation GAQ-1 (92.4%) and GAQ-2 (88.2%) responses of patients who had remained on tadalafil OaD throughout the observation differed by 2% or less from those for the overall cohort.

Safety data
Six serious adverse events (SAEs) were reported by 5 patients, all patients had used tadalafil OaD treatment throughout. SAEs included prostate cancer (1), worsening of benign prostate hyperplasia (1), cardiac failure (1), coronary artery stent insertion (1), and erysipelas (1) and accident (1). Investigators considered none of these SAEs as related to tadalafil OaD. The patient who experienced serious cardiac failure was discontinued from tadalafil OaD. The patient who experienced serious cardiac failure was discontinued from tadalafil OaD (outcome of event unknown). No deaths were reported during the study. Overall, 67 of 778 patients (8.6%) reported at least one adverse event during treatment with tadalafil OaD. Headache (1.3%), dyspepsia (0.5%) and BPH (0.5%) were reported most frequently (Table 5; all other adverse events were reported by ≤ 3 patients).

Discussion
This study (EDATE) represents the first observation of treatment continuation, effectiveness and tolerability in ED patients treated with tadalafil OaD in routine clinical practice. Time to discontinuation from start of tadalafil OaD treatment was chosen as primary outcome because this measure reflects satisfaction, which is the most important aspect for the patient, integrating compatibility with sexual activity patterns, effectiveness, psychosocial factors and tolerability, all of which may impact the treatment adherence of an individual patient.

While the median time to discontinuation of tadalafil OaD could not be estimated because of a lower than anticipated number of events, the 25th percentile was 31 weeks. After 2, 4 and 6 months, respectively, 94.0%, 88.3% and 86.3% of patients who had initiated or switched to tadalafil OaD at baseline were still continuing this treatment. In a previous RCT which assessed treatment adherence of 770 PDE5-inhibitor naïve patients who were randomised to tadalafil OaD, tadalafil PRN, or sildenafil PRN and were followed up for 24 weeks, median time to discontinuation of tadalafil OaD was 19 weeks, compared with 10 weeks for sildenafil PRN (23). At 2, 4 and 6 months respectively,
75.9%, 52.5% and 47.8% of randomised patients continued treatment with tadalafil OaD (23). Patients thus adhered longer to tadalafil OaD in the observational setting of EDATE. An important reason for this difference may be that patients in EDATE had chosen their preferred treatment at baseline, whereas patients in the RCT had been randomised to a particular drug or treatment regimen. Consistent with this interpretation, only 1.5% of all patients starting tadalafil OaD discontinued because they did not want to take an ED medication every day in EDATE, as opposed to 10.5% of patients randomised to tadalafil OaD (23). This may also explain the low percentage of patients switching to PRN treatment.

For patients treated previously with PDE5-inhibitors, lack of efficacy of their previous treatment, patient preference for OaD treatment (after discussing treatment options with the physician and/or preference based on prior information), the feeling that their previous medication controlled their sexual life, and partner request were the most important reasons for choice of tadalafil OaD (Table 2). For PDE5-inhibitor naïve patients, clinical experience of the investigator (i.e. physicians’ advice to the patient guiding patient choice) and patient preference were the most frequently recorded reasons for initiating tadalafil OaD treatment. Another key difference between the two studies assessing treatment adherence was that patients had to pay for their PDE5-inhibitor treatment in EDATE (ED treatment with PDE5-inhibitors is not reimbursed in the participating countries), while they were supplied with study drug for free during the RCT. Nevertheless, only 2.1% of all patients on tadalafil OaD reported “costs of medication” as reason for discontinuation in the observational EDATE study. It may be assumed that the participating patients were well informed regarding potential benefits and medication costs prior to the decision to start treatment. This may suggest a positive cost-benefit for the large majority of patients who continued treatment. The main reason for discontinuation of tadalafil OaD was lack of efficacy (hardness of erection), reported by 4.2% of all patients starting tadalafil OaD. As expected, this proportion was much lower when compared with the RCT, where 21.4% of PDE5-inhibitor naïve patients randomised to tadalafil OaD stated this reason (23).

Patients with ED diagnosed by their general practitioner on average adhered longer to OaD treatment than patients with ED diagnosed by an urologist (p < 0.001). We can only speculate about the reasons. General practitioners who agreed to participate in EDATE may primarily have been those with a special interest in sexual medicine, and therefore experienced in dealing with patients reporting sexual complaints. Also, general practitioners frequently have a long-standing relationship with their patients. This might have led to a more individual discussion with the patient on available treatment options and therefore to a higher probability of choosing the treatment suited best for the particular patients’ needs and expectations, thus resulting in a higher adherence.

Tadalafil OaD was confirmed to be effective in the large majority of patients, as demonstrated by significant improvements in IIEF-EF. LSmean scores increased by 7.1 points from baseline to 4–6 months (T3) after initiation of tadalafil OaD, exceeding the minimally clinically important difference (MCID) of four points (24), and were consistent with the 9.4-point increase observed with tadalafil OaD in the previous RCT (23). Overall, 86% of patients reported improvements in their ability to engage in sexual activity, consistent with 84% observed with tadalafil OaD in the RCT (25).

The percentage of patients who discontinued tadalafil OaD treatment because of adverse events reported in EDATE (2.8%) was close to that reported in the RCT (3.9%) (23). Headache was the most frequently reported adverse events in both studies. No new or unexpected safety signals associated with tadalafil OaD treatment in routine practice were detected.

Potential baseline factors which may contribute to treatment discontinuation (identified using the modelling approach) included age and duration of living arrangement, which may be related to the frequency of sexual activity (26).

EDATE not only provides the first results on tadalafil OaD treatment in routine practice, but also extends the knowledge on PDE5-inhibitor treatment in general gained from previous prospective observational studies. Comparing different PDE5-inhibitor regimen across different observational studies may be criticised because design and patient populations as well as definitions of continuation, persistence and adherence are different. Nevertheless, the comparison of continuation rates observed in a number of previous studies with different PDE5 inhibitors PRN may provide useful information.

In the European Erectile Dysfunction Observational Study (EDOS), 57.7% of all patients prescribed tadalafil PRN at baseline (regardless if naïve or previously treated) and followed up for 6 months remained on this treatment for 6 months; the corresponding rates in treatment-naïve patients only was 89% (tadalafil PRN), compared with 63–64%
Tadalafil OaD continuation and effectiveness

(sildenafil or vardenafil) (21). The corresponding values for the tadalafil OaD cohort of the current study EDATE were 78.3% (609 of 778 patients starting the observation) and 94.8% (398 of 420 naive patients completing the study). In another European observational study (DETECT), 84% of patients reported continued tadalafil PRN use at 12 months (27). Persistence of tadalafil PRN use at Month 6 was 71.6% and 68.8%, respectively, in two observational studies conducted in Latin America and Middle East/North Africa (28,29).

Although based on different studies, these data suggest that continuation rates after treatment with tadalafil OaD may at least be non-inferior compared with PRN regimens. This could result from a true advantage of the OaD regimen, but also from shared decision-making and more comprehensive patient information. Before starting OaD treatment, physicians might have taken more time to discuss the possible benefits and pitfalls of the various ED treatment approaches to identify the most appropriate regimen for each individual patient. Patients who made an informed decision together with their physicians and choose the most suitable treatment with respect to their preferences and needs (regarding dosing, duration of action and spontaneity of sexual activity) may be more likely to continue their treatment. This hypothesis would need confirmation by an interventional trial with standardised comprehensive patient information regarding the different treatment regimen, followed by either free patient choice of the PDE5 inhibitor regimen, or randomised treatment assignment.

Limitations of this study include bias caused by routine practice and preference of participating investigators, as suggested by the high proportion of patients starting with tadalafil OaD at baseline. To increase the external validity of our data, we aimed to minimise this potential source of bias by randomly selecting sites from a list of investigators expressing interest in participation and by asking sites to enrol patients consecutively. This site selection and enrolment process was a particular strength of the study. We cannot exclude that results were still biased because only sites and investigators with an interest to participate could be selected. In addition, patients who had chosen tadalafil OaD may have decided to participate in the study more frequently than patients starting PRN treatment because only patients starting with tadalafil OaD received additional postbaseline evaluations. As patients had to pay their treatment during the observational period, this might have biased the tadalafil OaD cohort towards patients with higher education and economic status.

In conclusion, 86.3% of men who started/switched to tadalafil OaD at baseline continued tadalafil OaD treatment for ≥ 6 months. IIEF-EF scores improved significantly, exceeding the MCID, with 91% of patients reporting improved erections and 86% reporting improved ability to engage in sexual activity at T3. The majority of study completers (91%) continued tadalafil OaD after the study. No new or unexpected safety signals associated with tadalafil OaD treatment in routine practice were detected.

If patients receive adequate information about the respective properties of treatments available and their appropriate use and are given the opportunity to choose an ED treatment suited to their individual needs and preferences, they may experience clinically relevant EF improvement and may likely be satisfied with their medication in routine practice. Detailed patient information, expectation-management and participative decision-making at the time of prescription might improve treatment adherence compared with an RCT setting.

Author Contributions

FB and HB designed the study. JB, DH and HP participated in data collection. FB drafted the article (supported by Trilogy Writing and Consulting GmbH). CH was responsible for statistics and data analysis. All authors contributed to data interpretation, critically revised the manuscript and approved the final version.

Acknowledgements

The study was funded by Eli Lilly and Company, Indianapolis, USA. We thank all patients who volunteered to participate in this trial and all study investigators for their contribution to data acquisition and patient care. We thank Julia Branicke, Eli Lilly and Company, for supporting the conduct of the study. We thank Hartwig Buettner and Kraig Kinchen for medical advice. We thank Clare Barker, Bruce Basson, Ann Gibb and Pepa Polavieja, all from Eli Lilly and Company, for statistical support and for their contributions to the statistical analysis plan. Statistical analyses were programmed by PSI CRO LTD, St. Petersburg, Russia. We thank Karin Helsberg, PhD, Trilogy Writing and Consulting GmbH, Frankfurt, Germany, for providing medical writing services on behalf of Eli Lilly and Company.
References

1. Goldstein I, Lew TF, Padma-Nathan H, Rosen RC, Steers WD, Wicker PA. Oral sildenafil in the treatment of erectile dysfunction. Sildenafil Study Group. N Engl J Med 1998; 338: 1397–404.

2. Brock GB, McMahon CG, Chen KK et al. Efficacy and safety of tadalafil for the treatment of erectile dysfunction: results of integrated analyses. J Urol 2002; 168: 1332–24.

3. Hellstrom WJ, Gittelman M, Karlin G et al. Vardenafil for treatment of men with erectile dysfunction: efficacy and safety in a randomized, double-blind, placebo-controlled trial. J Androl 2002; 23: 763–71.

4. Porst H, Giuliani F, Gliena S et al. Evaluation of the efficacy and safety of once-a-day dosing of tadalafil 5 mg and 10 mg in the treatment of erectile dysfunction: results of a multicenter, randomized, double-blind, placebo-controlled trial. Eur Urol 2006; 50: 351–9.

5. Montorsi F, Aversa A, Moncada I et al. A randomly assigned, double-blind, placebo-controlled, parallel study to assess the efficacy and safety of once-a-day tadalafil in men with erectile dysfunction who are naive to PDE5 inhibitors. J Sex Med 2011; 8: 2617–24.

6. Tsertsvadze A, Fink HA, Yazidi F et al. Oral phosphodiesterase-5 inhibitors and hormonal treatments for erectile dysfunction: a systematic review and meta-analysis. Ann Intern Med 2009; 151: 650–61.

7. Yuan J, Zhang R, Yang Z et al. Comparative effectiveness and safety of oral phosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol 2013; 63: 902–12.

8. Althof SE. When an erection alone is not enough: biopsychosocial obstacles to lovemaking. Int J Impot Res 2002; 14: 599–104.

9. Hatziychristou D, Mousidis K, Apostolidis A et al. Sildenafil failures may be due to inadequate patient instructions and follow-up: a study on 100 non-responders. Eur Urol 2005; 47: 518–22.

10. Porst H, Padma-Nathan H, Giuliani F, Anglin G, Varanese L, Rosen R. Efficacy of tadalafil for the treatment of erectile dysfunction at 24 and 36 h after dosing: a randomized controlled trial. Urology 2003; 62: 121–5.

11. Young JM, Feldman RA, Auerbach SM et al. Tadalafil improved erectile function at twenty-four and thirty-six hours after dosing in men with erectile dysfunction: US trial. J Androl 2005; 26: 310–8.

12. Eardley I, Montorsi F, Jackson G et al. Factors associated with preference for sildenafil citrate and tadalafil for treating erectile dysfunction in men naive to phosphodiesterase 5 inhibitor therapy: post hoc analysis of data from a multicentre, randomized, open-label, crossover study. BJU Int 2007; 100: 122–9.

13. Rubio-Aurioles E, Porst H, Kim ED et al. A randomized open-label trial with a crossover comparison of sexual self-confidence and other treatment outcomes following tadalafil once a day vs. tadalafil or sildenafil on-demand in men with erectile dysfunction. J Sex Med 2012; 9: 1418–29.

14. Forgue ST, Patterson BE, Bedding AW et al. Tadalafil pharmacokinetics in healthy subjects. Br J Clin Pharmacol 2006; 61: 280–8.

15. Rajfer J, Aliotta PJ, Steidle CP, Fitch WP, Zhao Y, Yu A. Tadalafil dosed once a day in men with erectile dysfunction. A randomized, double-blind, placebo-controlled study in the US. Int J Impot Res 2007; 19: 95–103.

16. Drishko R, Sorsaburu S, Wong D, Strawbridge A, McGill I. Safety, efficacy, and pharmacokinetic overview of low-dose daily administration of tadalafil. J Sex Med 2009; 6: 2039–48.

17. Rubio-Aurioles E, Kim ED, Rosen RC et al. Impact on erectile function and sexual quality of life of couples: a double-blind, randomized, placebo-controlled trial of tadalafil taken once daily. J Sex Med 2009; 6: 1314–23.

18. Althof SE, Rubio-Aurioles E, Kingsberg S, Zeiger H, Wong DG, Burns P. Impact of tadalafil once daily in men with erectile dysfunction—including a report of the partners’ evaluation. Urology 2010; 75: 1358–63.

19. Cappelleri JC, Rosen RC, Smith MD, Mishra A, Osterloh IH. Diagnostic evaluation of the erectile function domain of the International Index of Erectile Function. Urology 1999; 54: 346–51.

20. Rosen RC, Riley A, Wagner G, Osterloh IH, Kirkpatrick J, Mishra A. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49: 822–30.

21. Hatziychristou D, Haro JM, Martin-Morales A et al.; EDOS Group. Patterns of switching PDE5 inhibitors in the treatment of erectile dysfunction: results from the Erectile Function Observational Study. Int J Clin Pract 2007; 61: 1850–62.

22. Akaike H. (1973) Information theory and an extension of the maximum likelihood principle. In: Petrov BN and Caski F, eds. Proceedings of the Second International Symposium on Information Theory. Budapest: Akademiai Kiado, pp. 267–81.

23. Burat J, Büttnner H, Hatzimouratidis K et al. Adherence to initial PDE5 inhibitor treatment: randomized open-label study comparing tadalafil once a day, tadalafil on demand and sildenafil on demand in subjects with erectile dysfunction. J Sex Med 2013; 10: 1592–602.

24. Rosen RC, Allen KR, Ni X, Araujo AB. Minimal clinically important differences in the erectile function domain of the International Index of Erectile Function scale. Eur Urol 2011; 60: 1010–6.

25. Hatzimouratidis K, Büttner H, Burat J et al. Sexual self-confidence and spontaneity after initiation of treatment with tadalafil once a day, tadalafil on demand or sildenafil citrate on demand: a randomized open-label study in previously untreated patients with erectile dysfunction. Poster presented at the 15th Congress of the European Society for Sexual Medicine (ESSM), Amsterdam, The Netherlands, December 6–8, 2012.

26. Karraker A, DeLamater J, Schwartz CR. Sexual frequency decline from midlife to later life. J Gerontol B Psychol Sci Soc Sci 2011; 66: 502–12.

27. Roumeguère T, Verheyden B, Aryer S, Bitton A, Belger M, Schmitt H. DETECT study investigators. Therapeutic response after first month of tadalafil treatment predicts 12 months treatment continuation in patients with erectile dysfunction: results from the DETECT study. J Sex Med 2008; 5: 1708–19.

28. Rubio-Aurioles E, Reyes LA, Borregales L, Cairoli C, Sorsaburu S. A 6-month, prospective, observational study of PDE5 inhibitor treatment persistence and adherence in Latin American men with erectile dysfunction. Curr Med Res Opin 2013; 29: 695–706.

29. El-Meleigy A, Rabah D, Al-Mitwalli K et al. A 6-month, prospective, observational study of PDE5 inhibitor treatment persistence and adherence in Middle Eastern and North African men with erectile dysfunction. Curr Med Res Opin 2013; 29: 707–17.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Factors associated with the initial choice of tadalafil OaD at baseline (logistic regression analysis; 601 patients included in model, 478 (79.5%) chose tadalafil OaD).

Figure S2. Factors associated with switching from other PDE-inhibitor treatment to tadalafil OaD at baseline (logistic regression analysis; 319 patients included in model, 258 (80.9%) switched to tadalafil OaD).

Figure S3. Factors associated with continuation of tadalafil OaD treatment up to Month 6 (logistic regression model; 738 patients included in model, 570 (77.2%) remained on tadalafil OaD up to Month 6).

Table S1. Frequent Medical Histories (≥ 0.5% overall, Preferred Term Level).

Table S2. Frequent Pre-existing Conditions (≥ 1% overall, Preferred Term Level).

Paper received December 2013, accepted March 2014