# Population Dose-Response Model for Tadalafil in the Treatment of Male Erectile Dysfunction

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***Purpose.*** To determine the population dose-response relationship for tadalafil during on-demand (as-needed) administration for treatment of erectile dysfunction (ED).

***Methods.*** A total of 212 male patients with mild, moderate, or severe ED participated in a multicenter, randomized, double-blind, placebo-controlled, parallel-group study. Patients were randomized to receive placebo or 2, 5, 10, or 25 mg tadalafil, taken on demand over an 8-week period. Efficacy was assessed on the basis of questions 2 and 3 of the Sexual Encounter Profile (SEP) and questions 3 and 4 of the International Index of Erectile Function (IIEF) questionaires. These scores were modeled using logistic regression. A fifth patient response, the IIEF EF (erectile function) domain score, was modeled as a continuous variable.

***Results.*** The dose-response relationship for each efficacy variable was best described with an $E_{max}$ model, in which maximum effect increased with ED severity at baseline. Response scores increased substantially between 10 and 25 mg tadalafil doses, and the dose-response parameter estimates suggested possibly higher responses at even higher doses.

***Conclusions.*** Population dose-response modeling of all five oucome measures indicated that efficacy in all ED severity groups in the studied population generally increased across the 2 to 25 mg tadalafil dose range. Estimates of maximal improvement ($E_{max}$) in the IIEF EF domain score were 7.5, 11.4, and 16.3 points for patients with mild, moderate, and severe ED, respectively. Corresponding tadalafil doses to attain half-maximal improvement ($ED_{50}$ estimates) were 4.7 mg, 7.1 mg, and 10.1 mg.

**KEY WORDS:** Erectile dysfunction; tadalafil; dose-response modeling; population pharmacodynamics.

## INTRODUCTION

Erectile dysfunction (ED) has been defined by the National Institutes of Health Consensus Development Panel on Impotence and the American Urological Association as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance (1,2). ED is a prevalent condition (3,4), affecting an estimated 152 million men worldwide (5). Phosphodiesterase type 5 (PDE5) is a critical component of the nitric oxide (NO)–cyclic guanosine monophosphate (cGMP) signaling pathway responsible for smooth-muscle tone modulation in the penis (6–8). Inhibition of PDE5 amplifies the NO-mediated response to sexual stimulation, increasing intracellular concentrations of cGMP, which leads to relaxation of vascular and cavernosal smooth muscles and facilitates the achievement and maintenance of penile erection (9,10).

Tadalafil (IC351; Cialis; pyrazino[1',2':1,6]pyrido[3,4-b]indole-1,4-dione, 6-(1,3-benzodioxol-5-yl)-2,3,6,7,12,12a-hexahydro-2-methyl-,(6R,12aR)-) is a potent and selective reversible inhibitor of PDE5 that is now marketed in the USA, the European Union, and additional countries for the treatment of ED. The recommended starting dose of tadalafil varies across global markets, being generally 20 mg or 10 mg taken orally prior to anticipated sexual activity. The maximum recommended dosing frequency is once daily.

Studies with tadalafil in patients with ED have demonstrated enhanced erectile rigidity in the clinic setting, as well as efficacy and tolerability in the at-home setting (11–13). Efficacy of tadalafil treatment was assessed using the Sexual Encounter Profile (SEP) and International Index of Erectile Function (IIEF) questionnaires (14,15), the scores of which can be regarded as binary or ordered categorical variables, respectively. To analyze such efficacy variables as a function of dose or systemic exposure, logistic regression models are useful, as reported for previous population pharmacodynamic analyses (16–18). The sum of IIEF questions 1–5 and 15, denoted the "erectile function (EF) domain," ranges from 1 to 30 points and was treated as a continuous variable (19).

Population pharmacodynamic modeling was incorporated in early clinical development of tadalafil in order to help dose selection and identify patient characteristics that might influence efficacy, such as race, age, and ED etiology, including diabetes (20,21). Such modeling has proved to be beneficial in the development of several drug classes (22). The objectives of the population analysis described herein were to (i) establish the dose-response relationship across the 2 to 25 mg dose range, (ii) account for the interindividual variability in response, and (iii) identify patient characteristics accounting for variability in ED response. A secondary objective was to compare response outcomes assessed with either SEP questions 2 and 3 (SEP Q2 and Q3), IIEF questions 3 and 4 (IIEF Q3 and Q4), or the EF domain.

## METHODS

### Subjects

Two hundred twelve male patients with mild, moderate, or severe ED participated in the study. All patients and their partners provided written informed consent. The study was conducted at 10 centers in Canada, in accordance with the ethical principles of the Declaration of Helsinki, the applicable guidelines for good clinical practice, or the applicable laws and regulations of Canada, whichever provided greater

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**ABBREVIATIONS:** $ED_{50}$, dose that produces 50% of $E_{max}$; $E_{max}$, maximal effect; ED, erectile dysfunction; IIEF Q3 and Q4, International Index of Erectile Function, questions 3 and 4; IIEF EF domain, International Index of Erectile Function, erectile function domain; PDE5, phosphodiesterase type 5; SE%, standard error of the estimate expressed as a percentage of the estimate; SEP Q2 and Q3, Sexual Encounter Profile, questions 2 and 3; –2LL, NONMEM objective function value, –2 log(likelihood).

protection of the individual. Male patients older than 18 years of age in a stable, monogamous, and heterosexual relationship with a history of ED of at least 3 months' duration were eligible. ED was defined as an inability to achieve or maintain an erection sufficient for satisfactory sexual performance (1,2) and was classified on the baseline IIEF EF domain score as: 1 to 10, severe ED; 11 to 16, moderate ED; and 17 to 30, mild ED (19,23).

Patients with ED caused by untreated endocrine disorders, history of radical prostatectomy with failure to achieve any erection, pelvic surgery, significant penile curvature, prior unsuccessful treatment with PDE5 inhibitors, history of HIV infection, poorly controlled diabetes mellitus, or clinically significant hepatic, renal, cardiovascular, or central nervous system disease during the last 6 months were excluded from the study. Treatments with nitrates, azole antifungals, warfarin, erythromycin, and/or antiandrogens were not permitted at any time during the study. Treatment with any other ED therapy was not allowed for at least 4 weeks prior to treatment and during treatment. The main characteristics of the patients at baseline are listed in Table I.

## Study Design

This study was designed as a multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase II study. It consisted of a 4-week, treatment-free run-in period followed by a treatment period of 8 weeks. During the run-in period, at least four sexual intercourse attempts were required, and the first SEP diary was provided to patients and partners. At the end of the run-in period (visit 2), the SEP diary data were collected, the baseline IIEF scores were obtained, and patients were randomized to placebo or 2, 5, 10, or 25 mg tadalafil. All tablets were identical in appearance, shape, smell, and taste. Patients were permitted to take one oral dose of study medication (with 180 ml water) prior to expected sexual intercourse, without any advice about the interval between dosing and sexual attempt, and they were instructed not to take more than one dose in any 24-h period. Following randomization, patients visited the clinic every 2 weeks (visit 3, 4, 5, and 6). At visit 2, 3, 4, and 5, each patient was provided with 16 individual blister packs, each pack containing one dose; patients were asked to return all used and unused blister packs, and accountability records were maintained.

## Pharmacodynamics

Pharmacodynamic models were developed for the following five efficacy variables: answers to SEP Q2 and Q3; answers to IIEF Q3 and Q4; and the IIEF EF domain determined as the sum of scores obtained in questions 1–5 and question 15 (19). Patients were instructed to complete the SEP diary after each sexual encounter, and the diaries were collected at each visit. IIEF questionnaires were given to each patient at visit 2, 4, and 6 (after 8 weeks of treatment).

SEP Q2 and Q3 inquire "Were you able to insert your penis into the partner's vagina?" and "Did your erection last long enough for you to complete intercourse with ejaculation?," respectively, and both can be answered with "Yes" or "No." For modeling, 1 was assigned to a "yes" answer and 0 was assigned to a "no" answer. Q3 and Q4 of the IIEF inquire "Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?", and "Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection

**Table I.** Characteristics at Baseline for All Patients Represented in the Population Modeling Data Set

| Characteristic | Class | Mean (n = 212) or number of patients (SD or % total) |
|---|---|---|
| Age (years) | | 58 (10.1) |
| Weight (kg) | | 87 (14.5) |
| Calculated creatinine clearance (Cockroft-Gault formula; ml/min) | | 111 (34.0) |
| Ethanol (units consumed/week) | | 3.64 (4.2) |
| Race | Caucasian | 194 (92%) |
| | African descent | 10 (5%) |
| | Asian | 7 (3%) |
| | Other | 1 (<1%) |
| Smoking status | Nonsmoker | 172 (81%) |
| | Current smoker | 40 (19%) |
| Cardiovascular conditions* | None | 119 (56%) |
| | Currently active | 85 (40%) |
| | History only | 8 (4%) |
| Diabetes | No | 168 (79%) |
| | Yes | 44 (21%) |
| ED severity | Mild | 93 (44%) |
| | Moderate | 52 (25%) |
| | Severe | 67 (32%) |

| ED severity by treatment: | Placebo | 2.5 mg | 5 mg | 10 mg | 25 mg |
|---|---|---|---|---|---|
| Mild | 19 (46%) | 20 (48%) | 15 (34%) | 19 (45%) | 20 (46%) |
| Moderate | 10 (24%) | 8 (19%) | 14 (32%) | 12 (29%) | 8 (19%) |
| Severe | 12 (29%) | 14 (33%) | 15 (34%) | 11 (26%) | 15 (35%) |

* One or more of: coronary artery disorder, hypertension, myocardial infarction, arrhythmia, hypercholesterolemia, angina pectoris, ED, erectile dysfunction.

after you had penetrated (entered) your partner?", respectively. The responses to these two questions were rated on a scale of 0 to 5, where 1 indicates the worst and 5 the best performance, with 0 indicating no intercourse attempt intercourse.

### Data

Two hundred twelve patients were randomized. The distribution of patients per dose group was as follows: placebo (n = 41), tadalafil 2 mg (n = 42), tadalafil 5 mg (n = 44), tadalafil 10 mg (n = 42), and tadalafil 25 mg (n = 43). Of the 212 patients, 202 patients completed the study and 10 patients discontinued prior to study completion due to adverse events (n = 2), personal conflict or other patient decision (n = 4), protocol violation (n = 2), protocol entry criteria not met (n = 1), and lost to follow-up (n = 1). A total of 5,182 SEP Q2 scores and 5,177 SEP Q3 scores were available in the modeling data set, with a number of recorded scores similar across visits. On average, approximately five SEP scores per patient had been recorded in each visit interval. A total of 212, 208 (209 for Q4) and 205 observations of each IIEF score were recorded at baseline, visit 4, and visit 6, respectively.

### Data Analysis

Each pharmacodynamic efficacy variable was modeled separately using the NONMEM version V software for nonlinear mixed effects modeling (24). The Laplacian estimation method with the "Likelihood" option was used. Selection between models was based on standard errors of parameter estimates, goodness-of-fit plots, as well as the minimum value of the NONMEM objective function value [–2 log(likelihood); –2LL]. A decrease >7.88 points in –2LL was considered significant ($p < 0.005$) for two nested models differing by one parameter.

### Categorical Responses

Logistic regression was used to analyze the dichotomous (SEP Q2 and SEP Q3) and the ordered categorical (IIEF Q3 and IIEF Q4) variables following the approach described by Sheiner (16) and by Mandema and Stanski (25) for pain relief measures. In brief, the logistic regression model is represented as:

$$P_{Yij} = \frac{e^{L}}{1 + e^{L}} \tag{1}$$

where $P_{Yij}$ represents either (i) the probability of getting an observation (Y) equal to a certain score $m$ (SEP Q2, Q3) or (ii) the probability of getting a score $\geq m$ (IIEF Q3 and Q4) in the $i$th individual at the $j$th visit. An individual patient response was modeled as a conditional probability $P(Y_{ij} = m|\eta_i)$, where $\eta_i$ is the individual random effect. The set of individual $\eta$ values is assumed to be symmetrically distributed around 0 with variance $\omega^2$. In the case of IIEF Q3 and IIEF Q4, the probability of having score $m$ was coded as:

$$P(Y_{ij} = m|\eta_i) = P(Y_{ij} \geq m|\eta_i) - P(Y_{ij} \geq (m+1)|\eta_i) \tag{2}$$

The logit (L) within Eq. 1 combines the contribution of baseline, placebo, and drug dose effects on the probability as:

$$L = f_{\text{baseline}}(m) + g_{\text{placebo}}(time) + h(dose) + \eta_i \tag{3}$$

where $f_{\text{baseline}}(m)$ describes the distribution of baseline scores and has the form $\sum_{k=1}^{m} \beta b$, where $\beta_k$ ($k = 1$ for SEP Q2, Q3 and k = 1,…,5 for IIEF Q3, Q4) are the parameters defining the baseline probabilities of having a score m or $\geq m$.

To account for a placebo effect ($g_{\text{placebo}}$), various time-dependent ($E_{max}$ type, biexponential [25]) or visit-dependent functions were tested. Various $E_{max}$, sigmoidal $E_{max}$, and re-parameterized $E_{max}$ models were explored to describe the dose-effect relationship [$h(dose)$] (26). An overall random effect as represented in Eq. 3 was estimated. For SEP Q2 and SEP Q3, possible model enhancement by allowing for inter-individual (patient-to-patient) variability in the $E_{max}$ and/or slope ($E_{max}/ED_{50}$) parameters was tested. Interoccasion (visit-to-visit) variability in SEP Q2 and SEP Q3 responses was also investigated (27).

Model development proceeded sequentially from the baseline model, to the placebo model, to the drug dose model, and finally any significant covariate effect was incorporated. The baseline model was based on observations at visit 2. Placebo effects were explored using all observations for all treatment groups at visit 2 (for the best estimate of baseline scores), as well as the observations for the placebo group at the following visits. Drug and covariate effects were evaluated on the basis of all observations from the study. At each development stage, all model parameters were estimated simultaneously.

Covariate effects were explored by a forward selection and backward elimination process once the baseline, placebo, and dose-effect models had been developed. Beginning with the covariate that caused the largest –2LL drop when tested individually, the significant covariates were incorporated one at a time, until the full covariate model was obtained. If the additional covariate did not significantly improve the model, it was discarded. Subsequently, covariates were removed one at a time. If the covariate could be eliminated with only an insignificant –2LL change, then it was discarded. This backward elimination process continued until a final model with only the significant covariates was obtained. In addition to the covariates listed in Table I, the following factors were tested for significance: height, body mass index, γ-glutamyl transferase, alanine transaminase, aspartate transaminase, and alkaline phosphatase, although none was expected to affect any response variable. Diuretics, calcium channel blockers, and angiotensin-converting enzyme inhibitors were used by more than 10% of the patients throughout the study and were selected for evaluation as plausible covariates of response variables. Correlations between ED at baseline and other patient characteristics were explored prior to modeling; only diabetic status and ED severity were highly correlated.

The predictive performance of the model was checked by comparing the predicted population mean probability with the mean raw probability that was computed by dividing the number of observed scores equal to $m$ (for SEP) or greater than $m$ (for IIEF) by the total number of scores for the dose group. To obtain the predicted population mean probabilities, 100 data sets were simulated with the final model such that numbers of patients, dosing events, observations, and covari-

ates were the same as in the original data set. The number of predicted scores equal to *m* (SEP) or greater than *m* (IIEF) divided by the total number of predicted scores gave the typical predicted probability.

Because several observations were obtained in each individual and visit for SEP Q2 and Q3, raw vs. predicted probability plots could be generated for individual patients. Here, raw probability was the number of observed scores equal to m divided by the total number of scores for that patient and visit. Individual model predicted probabilities were obtained by simulating one data set using empirical Bayesian estimates of the model parameters for each individual, and the respective ratios were calculated as described for the raw data ratios.

### Continuous Response

The IIEF EF domain scores (1 to 30) were treated as a continuous variable. The dose-response model was developed directly using all IIEF EF domain data (all visits and patients) in order to estimate all fixed and random effect parameters simultaneously. First, a baseline score for each patient was estimated assuming no drug effect, and then a drug effect was introduced using an $E_{max}$ model. Finally, parameters allowing for an effect of placebo were tested for significance. The first-order estimation method of NONMEM was used. After selection of the baseline, placebo, and drug effects models, covariate effects were explored as described above.

Predictive performance was evaluated by comparing the raw data means across dose to the predicted mean responses for the "typical" patient. Furthermore, 100 data sets representative of the original data set were simulated with the final population model. Prediction error for each observation was calculated as 100 × (observed score – predicted score)/observed score (28). The median prediction error and the median absolute prediction error were used to evaluate bias and precision of the final population model.

## RESULTS

The raw data probabilities for SEP Q2 and Q3 and IIEF Q3 and Q4, as well as the distribution of IIEF EF domain scores, at baseline and during treatment (all visits combined) revealed a clear, dose-dependent improvement in sexual performance during tadalafil treatment (Fig. 1). For example, the probability for successful penetration (SEP Q2) increased from 60% to 80% when the dose was increased from 2 to 25 mg. The shape of the dose-response curve for these categorical responses is difficult to discern by inspection. The continuous IIEF EF domain data suggested a nonlinear, saturable response typically characterized with an $E_{max}$ model.

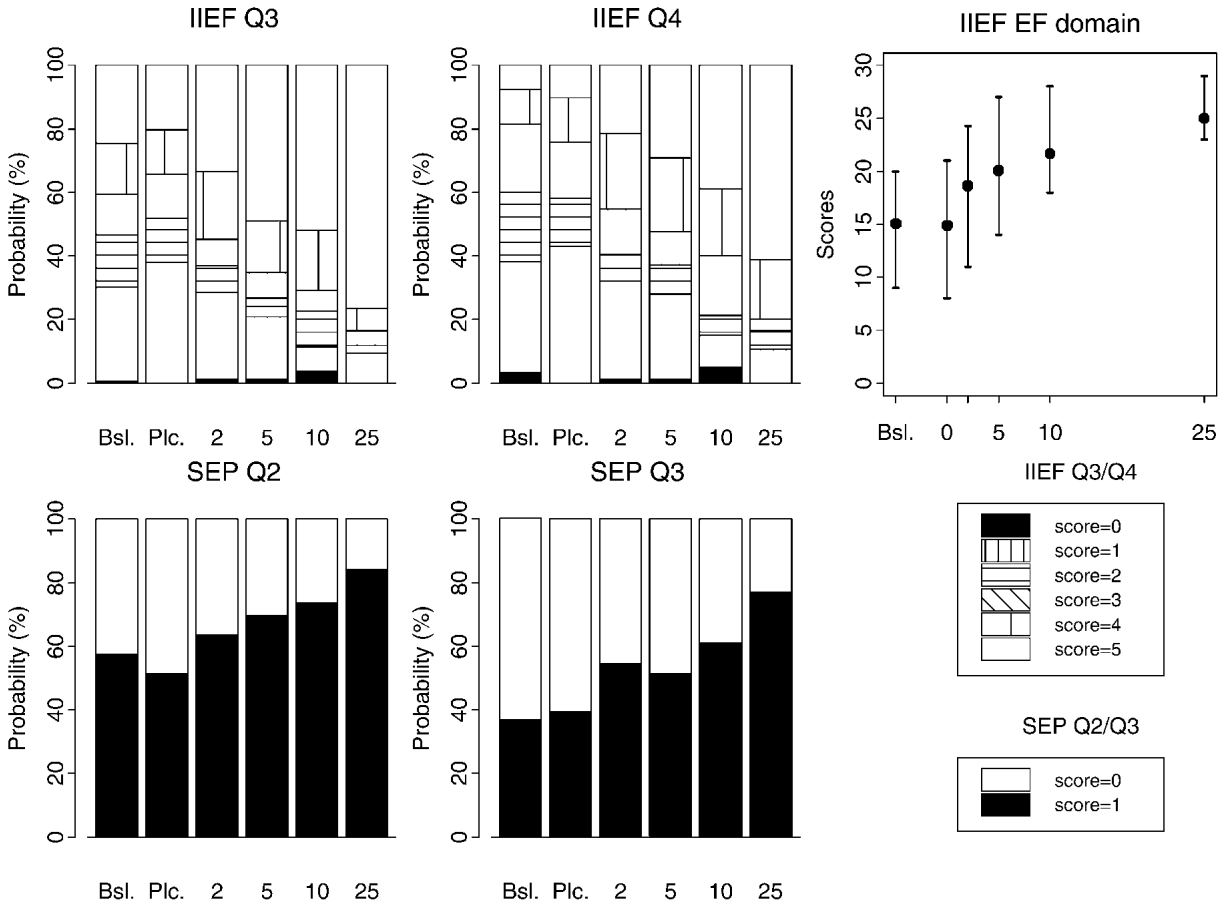


**Fig. 1.** Raw data for the five efficacy variables SEP Q2, SEP Q3, IIEF Q3, IIEF Q4, and IIEF EF domain at baseline under placebo and in the 2-, 5-, 10-, and 25-mg dose groups. Each bar is divided in regions proportional to the number of patients exhibiting the various scores. For the IIEF EF domain, the mean and the 25% and 75% percentiles are given. (Bsl., baseline; Plc., placebo; EF, erectile function; IIEF, International Index of Erectile Function; SEP, Sexual Encounter Profile; Q, question).

Results for placebo and each active dose group were essentially similar across visits (data not shown), except for a slightly higher proportion of SEP Q3 scores of 1 at visits 5 and 6.

The raw data indicated that the placebo effect was negligible as measured by change from the baseline scores for all patients (Fig. 1). This finding was also obvious from comparison of SEP and IIEF responses for placebo patients during the treatment phase relative to their own baseline values (data not shown). No statistically significant placebo effect (above baseline) was detected for any response variable by the selection criteria used during population model development.

Population pharmacodynamic models were developed for each of the five response variables independently. In each case, the tadalafil treatment effect was well described with an $E_{max}$ model (Tables II, III, and IV). For each SEP response, one baseline parameter was fixed to 0 (denoting a probability of 50%) in the final model because estimates were close to 0 and had high standard errors and because this was accomplished with negligible (<3.84; $p > 0.05$) increase in the –2LL value.

Deletion of the treatment effect from the model for each variable resulted in highly significant increases in –2LL values (from 152 to 642 points across the five response variables), indicating that tadalafil is effective in ED. Furthermore, the dose-dependency of the treatment effect was shown to be highly significant in each model. Only in the case of SEP Q3 was it necessary to account for time dependency in the estimate of tadalafil potency (Table II).

Quantification of patient-to-patient variability is a basic property of a population model. Such interindividual variability was introduced as a single random additive effect in the logit function of the categorical response models; more complex variance structures were not supported by the data. Although the interindividual variability estimates appear large ($\omega^2$ = 2.1 to 4.85; Tables II and III), the logit structure does not allow straightforward interpretation of this parameter. Inclusion of interoccasion variability in the SEP Q2 and Q3 models, accounting for slight variation in response within a patient from occasion to occasion, improved goodness-of-fit statistics. Interindividual variability in IIEF EF domain response was best described as a random exponential effect on slope ($E_{max}/ED_{50}$), indicating differences across patients in the tadalafil dose for half-maximal effect. Residual error was modeled as a random additive effect.

Severity of ED at baseline had an obvious impact on raw data probabilities and was, as expected, a significant covariate in all five population models. The best fits to the categorical data were obtained when ED severity was included twice in the model; firstly as a covariate of the baseline probability of a score equal to *m* (SEP) or greater than *m* (IIEF); and secondly as a covariate of $E_{max}$ (Tables II and III). Inclusion of ED severity on the baseline probabilities accounted for a large portion of patient-to-patient variability as assessed by decreases in the $\omega^2$ estimates from 10.7 to 4.85 (SEP Q2), 6.98 to 4.31 (SEP Q3), 8.04 to 2.1 (IIEF Q3), and 7.43 to 3.05 (IIEF Q4). Modeling the influence of ED severity on the slope parameter ($E_{max}/ED_{50}$) rather than $E_{max}$ led to inferior models. In the case of the IIEF EF domain, the baseline was described by the actual score and no random variance term was needed to account for interindividual variability in the baseline. Baseline ED severity classification was a strong covariate of maximal increase in score, as evident by increasing $E_{max}$ estimates with increasing severity (Table IV).

Standard errors suggested that model parameters were estimated with reasonable precision (Tables II, III, and IV).

**Table II.** Parameter Estimates of the SEP Q2 and SEP Q3 Models

| Parameter | SEP Q2 estimate (SE%) | SEP Q3 estimate (SE%) |
|---|---|---|
| $\beta_1$ (mild ED) | 2.98 (11) | 0 fixed |
| $\beta_1$ (moderate ED) | 0 fixed | –1.53 (17) |
| $\beta_1$ (severe ED) | –4.15 (12) | –4.38 (11) |
| $E_{max}$ (mild and moderate ED) | 1.38 (30) | 2.62 (23) |
| $E_{max}$ (severe ED) | 5.11 (15) | 5.11 (21) |
| Slope | | |
| (visits 3 and 4) ($mg^{-1}$) | 2.47 (58.3) | 0.817 (66) |
| (visits 5 and 6) ($mg^{-1}$) | 2.47 (58.3) | 1.83 (74) |
| $\omega^2$ | 4.85 (16) | 4.31 (15) |
| $\kappa^2$ | 1.45 (25) | 0.922 (25) |

SE%, standard error as a percentage of the parameter estimate; $\beta_1$, parameters defining the baseline probabilities of having a score of 1; slope = $E_{max}/ED_{50}$; $\omega^2$, variance of patient-specific random effect in response; $\kappa^2$, variance of interoccasion (patient-specific) random effect in response; ED, erectile dysfunction; SEP, Sexual Encounter Profile.

**Table III.** Parameter Estimates of the IIEF Q3 and IIEF Q4 Models

| Parameter | IIEF Q3 estimate (SE%) | IIEF Q4 estimate (SE%) |
|---|---|---|
| $\beta_1$ (mild ED) | 9.88 (11) | 8.86 (13) |
| $\beta_1$ (moderate ED) | 6.22 (13) | 6.32 (17) |
| $\beta_1$ (severe ED) | 3.86 (16) | 3.02 (17) |
| $\beta_2$ | –5.54 (14) | –6.02 (17) |
| $\beta_3$ | –1.37 (13) | –1.49 (12) |
| $\beta_4$ | –1.11 (15) | –1.51 (11) |
| $\beta_5$ | –1.5 (12) | –1.66 (11) |
| $E_{max}$ (mild ED) | 2.25 (37) | 3.45 (32) |
| $E_{max}$ (moderate ED) | 7.38 (38) | 3.45 (32) |
| $E_{max}$ (severe ED) | 7.38 (38) | 6.83 (23) |
| Slope ($mg^{-1}$) | 0.538 (44) | 1.35 (81) |
| $\omega^2$ | 2.1 (26) | 3.05 (29) |

$\beta_k$ (k = 1, . . ., 5), parameters defining the baseline probabilities of having a score $\geq k$; slope = $E_{max}/ED_{50}$; $\omega^2$, variance of patient-specific random effect in response; ED, erectile dysfunction.

**Table IV.** Parameter Estimates of the Models for IIEF EF Domain

| Parameter | Estimate (SE%) |
|---|---|
| $E_{max}$ (mild ED, IIEF EF domain score) | 7.53 (12) |
| $E_{max}$ (moderate ED, IIEF EF domain score) | 11.4 (10) |
| $E_{max}$ (severe ED, IIEF EF domain score) | 16.3 (10) |
| Slope (IIEF EF domain score/$mg^{-1}$) | 1.61 (16) |
| Interindividual variability in slope as a coefficient of variation | 6.7 (26) |
| Additive error (SD of IIEF EF domain score) | 2.59 (17) |

ED, erectile dysfunction; IIEF, International Index of Erectile Function.

Close agreement between predicted (simulated with the model) and observed probabilities for individual patients was demonstrated for SEP Q2 and Q3, as well as for EF domain scores (Fig. 2). Median prediction error (–0.9%) and median absolute prediction error (19%) for the EF domain scores indicated lack of bias and reasonable precision.

For all five outcome measures, maximal treatment effect ($E_{max}$) increased with severity of ED at baseline, indicating that patients with severe ED had higher potential for incremental improvement with tadalafil therapy than did patients with moderate or mild ED. Population mean predictions described the central tendency of the mean raw data probabilities and scores as a function of tadalafil dose and ED severity classification (Fig. 3). There was a substantial increase in treatment response between 10 mg and 25 mg tadalafil doses.

Categorical response variables can also be modeled as a function of systemic exposure rather than dose (16,25). Tadalafil exposure is essentially proportional to dose in the 2 to 25 mg range. Because SEP Q2 and Q3 responses (unlike IIEF scores) reflect a patient's acute response to tadalafil treatment, SEP scores were used to explore exposure (area under the curve [AUC] or $C_{max}$ estimates) as a predictor variable (results not shown). An AUC value based on plasma tadalafil concentration data from time of dosing until the sexual encounter was calculated for each patient from a population pharmacokinetic model developed separately. No evidence was found in this exploratory analysis that $C_{max}$ or this partial AUC was any better than dose for predicting either the population response or variability in responses across patients, suggesting that variability has a pharmacodynamic rather than pharmacokinetic basis.

## DISCUSSION

The relationships between tadalafil dose taken "on demand" and each of five outcome measures of ED were characterized with a population pharmacodynamic modeling approach that accounted for variability in response across patients.

Logistic regression models were used to analyze SEP Q2 and Q3 scores as dichotomous variables as well as IIEF Q3 and Q4 scores as ordered categorical variables. The IIEF EF domain score was modeled as a continuous variable. Patient-to-patient variability in these responses was estimated, and a substantial part of this interindividual variability was attributable to severity of ED at baseline. The population models were consistent in structure across the five efficacy variables and were essentially similar in demonstrating efficacy in all severity groups (Fig. 3). In all models, the placebo effect expressed as a change from the baseline probability or score was shown to be negligible, and the dose-response relationship was best described by a pharmacologically relevant $E_{max}$ model. Severity of ED at baseline (by an *a priori* classification) was a significant covariate of the baseline probability, as well as the $E_{max}$. The models all indicate that the magnitude of improvement in performance attributable to tadalafil increased with severity of ED prior to treatment (the greater the deficit, the greater the improvement possible), although the *absolute* performance at any dose level was the highest for the least severely affected men. Greater incremental improvement in erectile function in more severely affected patients was also concluded by Brock *et al.* (13) based on their

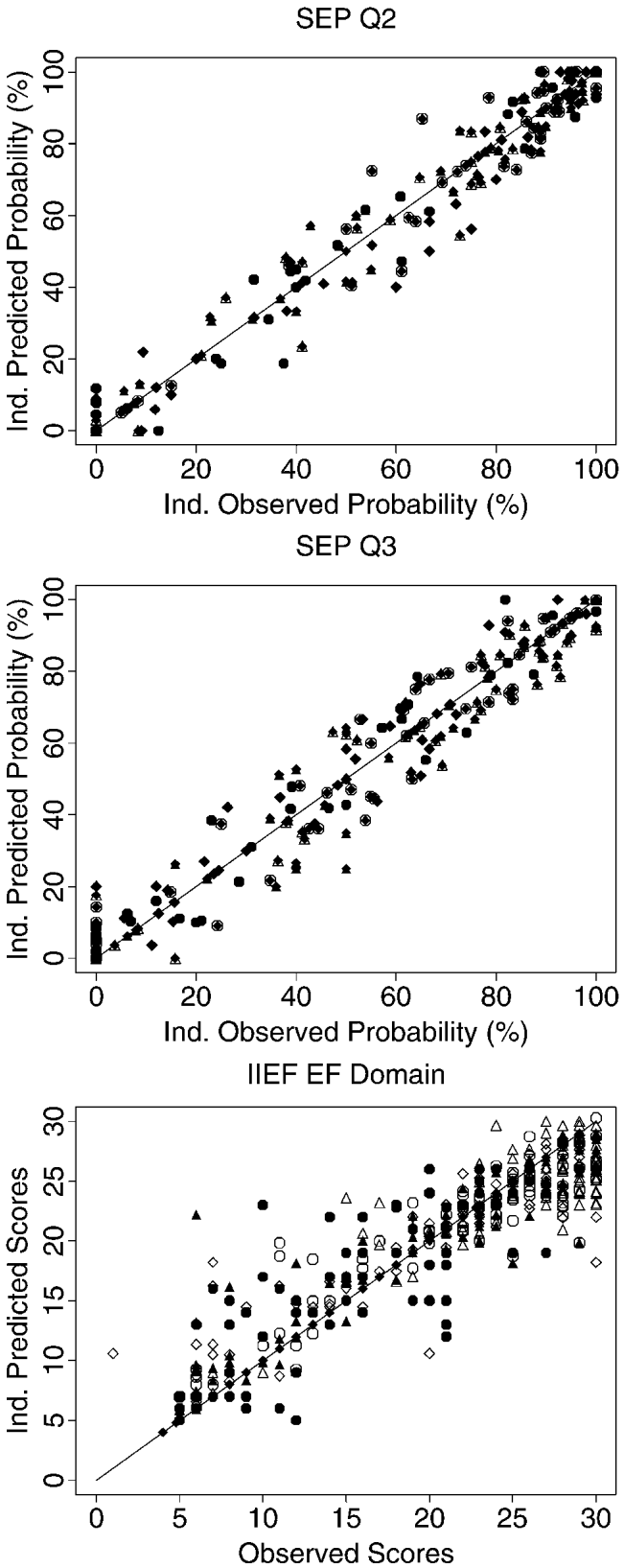


**Fig. 2.** Comparison of the individual predictions from the population pharmacodynamic models to the individual observations for SEP Q2 and SEP Q3 (probability Y = 1), as well as for IIEF EF domain. (♦ Baseline; ● placebo; ▲ 2 mg; ◊ 5 mg; ○ 10 mg; Δ 25 mg; EF, erectile function; IIEF, International Index of Erectile Function; SEP, Sexual Encounter Profile; Q, question).

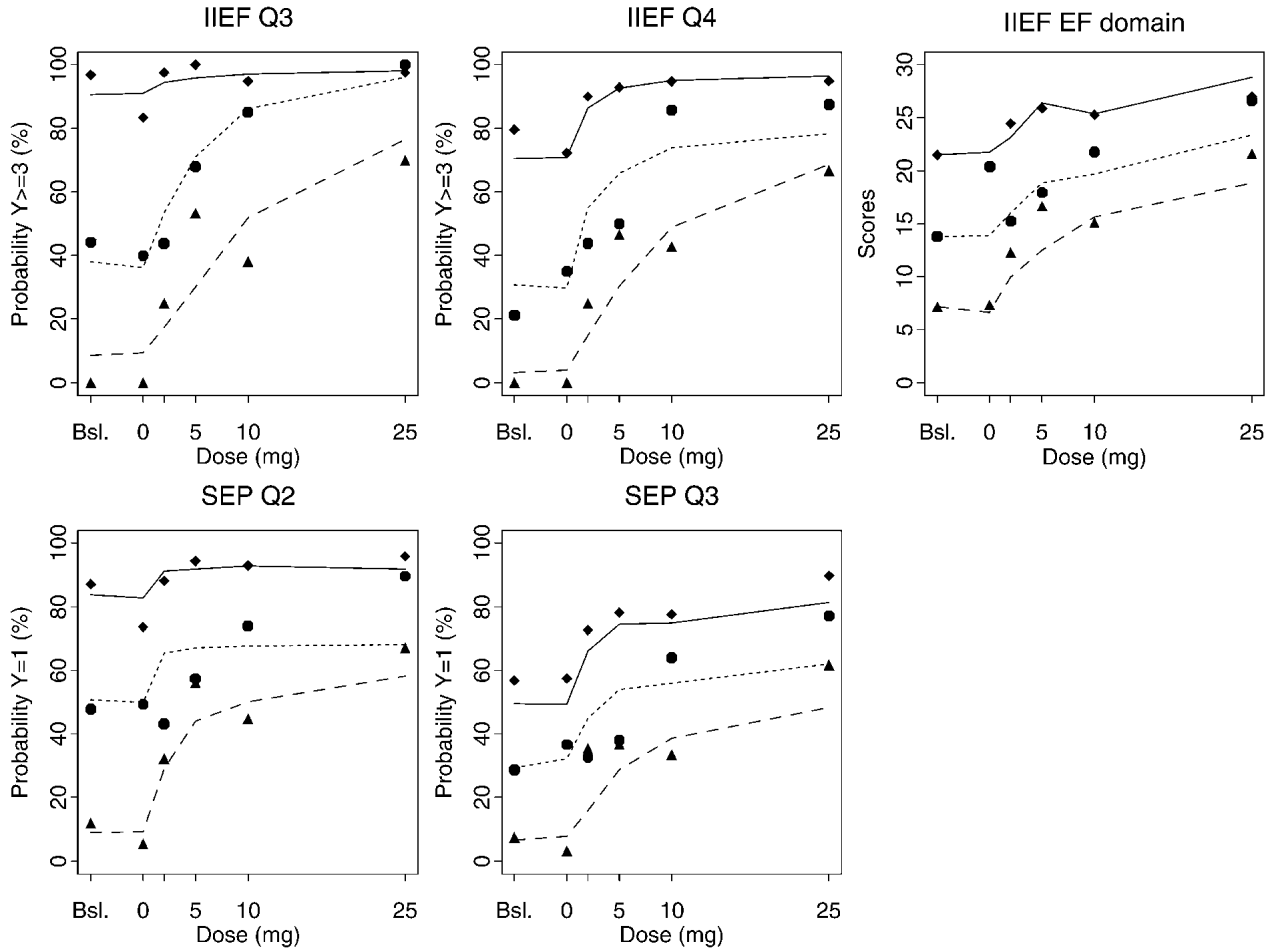


**Fig. 3.** Fit of the tadalafil dose-response model predictions to the observed raw data. The lines are the typical model predictions, and the symbols represent the raw mean data for patients with severe (▲), moderate (●), or mild (♦) ED at baseline. (Bsl., baseline; EF, erectile function; IIEF, International Index of Erectile Function; SEP, Sexual Encounter Profile; Q, question).

integrated statistical analyses of five other trials. No other significant covariate was found. Diabetic status and ED severity were highly correlated, with most diabetic patients having severe ED. This partial confounding of variables compromised identification of any independent effect of diabetes on treatment response. Age, weight, smoking status, history of alcohol consumption, and cardiovascular conditions had negligible effects on the tadalafil dose-response relationships.

Given inherent differences between analyses of dichotomous, ordered categorical, and continuous variables, and the fact that baseline and $E_{max}$ parameters may operate on the logit function of the probability models, head-to-head comparison of parameter estimates across models is not straightforward. The tadalafil $ED_{50}$ estimates computed as $E_{max}$/slope are compared in Table V for each efficacy variable by ED severity classification at study entry. For SEP and IIEF, $ED_{50}$ indicates the dose required to achieve one-half of $E_{max}$ in the logit function, not the half-maximal probability of response. The $ED_{50}$ values for IIED EF domain, along with the predicted dose-response curves for all five outcome measures

**Table V.** Characteristics of the Final Models for SEP Q2, SEP Q3, IIEF Q3, IIEF Q4, and IIEF EF Domain

| | Model characteristics | | | | |
|---|---|---|---|---|---|
| Response variable | Drug-effect model | $ED_{50}$ (mg) mild ED | $ED_{50}$ (mg) moderate ED | $ED_{50}$ (mg) severe ED | Placebo |
| SEP Q2 | $E_{max}$ | 0.6 | 0.6 | 2.1 | No |
| SEP Q3 | $E_{max}$ (Visit 3, 4) | 3.2 | 3.2 | 6.3 | No |
| | (Visit 5, 6) | 1.4 | 1.4 | 2.8 | No |
| IIEF Q3 | $E_{max}$ | 4.2 | 13.7 | 13.7 | No |
| IIEF Q4 | $E_{max}$ | 2.6 | 2.6 | 5.1 | No |
| IIEF EF domain | $E_{max}$ | 4.7 | 7.1 | 10.1 | No |

ED, erectile dysfunction; $ED_{50}$, dose that produces 50% of $E_{max}$.

(Fig. 3) indicate that a 10-mg dose is too low to achieve maximal efficacy in some patients.

To illustrate differences in $ED_{50}$ estimates for a given severity group, the increases in drug response for a dose increment from 10 to 25 mg were calculated using the typical model predicted probabilities. The probability (%) to get a score of 1 (success) for SEP Q2 and Q3 in a patient with severe ED increased by 8.0 and 9.7 percentage points, respectively. The incremental percentages to get a score $\geq 3$ (success half the time) for IIEF Q3 and Q4 were 24.6% and 19.7%, respectively. The corresponding increment for IIEF EF domain going from 10 to 25 mg was 3.5 points or 11.7% of the score range. Thus, all five efficacy variables supported the conclusion that the probability of successful sexual performance at 25 mg exceeded that at 10 mg.

The SEP Q2, SEP Q3, and IIEF EF domain scores may be the most appropriate for future efficacy trials. The combination of these three outcome measures captures acute response to tadalafil treatment (SEP Q2, Q3) as well as the measurement of treatment response over a period of 4 weeks (IIEF EF domain). All three variables support comparisons of typical values (population) of predictions, as well as individual model predictions, to the raw data (Figs. 2 and 3). Furthermore, EF domain allows the assignment of interindividual variability to specific pharmacodynamic parameters.

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