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Research Paper

Modeling and Simulation of Sexual Activity Daily Diary Data of Patients with Female Sexual Arousal Disorder Treated with Sildenafil Citrate (Viagra®)

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Purpose. To develop a model to explore the dose-response of sildenafil citrate in patients with female sexual arousal disorder (FSAD) based on telephone sexual activity daily diary (TSADD) data obtained in double-blind, placebo controlled clinical studies.
Materials. Data were available on 614 patients with FSAD. A parametric model (Weibull distribution) was developed to describe the probability density function of the time between sexual events. Orgasm satisfaction scores and overall sexual satisfaction scores were simultaneously modeled as ordered categorical variables. Simulations were performed to evaluate the expected clinical response in patients with FSAD.
Results. The expected time between sexual events was approximately 3.5 days. Satisfaction scores increased with time to achieve a plateau after 3 to 4 weeks on treatment. The expected probability of satisfying orgasm (score of 3 and higher) ranged from 34.7% for placebo to 41.6% for 100 mg sildenafil citrate. Treatment effect (difference from placebo) was 6.9% for 100 mg sildenafil citrate, ranging from 0.6 to 24.7% for testosterone levels of 0.1 to 4.0 pg/ml. The treatment effect in postmenopausal women was larger than in premenopausal women.
Conclusion. A modeling and simulation framework to support drug development in FSAD was developed. Sildenafil citrate demonstrated a dose-dependent effect in patients with FSAD.

KEY WORDS: female sexual arousal disorder; modeling and simulation; NONMEM; sildenafil citrate.

INTRODUCTION

Pfizer has been engaged in a development program for sildenafil citrate (Viagra®) in female sexual arousal disorder (FSAD) since 1996. Sildenafil citrate is an orally active, potent and selective inhibitor of cyclic guanosine monophosphate (cGMP) specific phosphodiesterase type 5 (PDE5), approved for the treatment of male erectile dysfunction (1). Experimental evidence suggests that the nitric oxide-cGMP pathway may be important in producing clitoral engorgement, pelvic vasocongestion and vaginal lubrication thus enhancing the female sexual arousal response (2,3). In pilot studies, sildenafil citrate was found to be effective in enhancing genital blood flow and vaginal and clitoral engorgement in premenopausal healthy women (4) and in premenopausal and postmenopausal woman with FSAD (5). Caruso *et al.* (6) demonstrated an improvement of sexual performance (subjective arousal and orgasm) in a short-term (4 weeks) double-blind, cross-over study of sildenafil citrate 25 and 50 mg and placebo in 53 premenopausal patients with FSAD. However, several large double blind placebo controlled outpatient parallel group studies of longer duration (8–12 weeks) provided inconsistent results. Some of these studies were conducted in special patient groups. Two 12-week parallel-group, double-blind studies, in which patients were randomized to receive 10–100 mg sildenafil citrate or placebo, did not show any benefit of sildenafil citrate over placebo (7). These studies were conducted in a patient population of premenopausal and postmenopausal women (n = 781) with only half of the patients having a primary diagnosis of FSAD. In one study (8), efficacy was established in a sub-group of post-menopausal women with FSAD who had physiologic levels of estrogen and testosterone. The covariate analysis in this study showed a highly significant overall treatment effect in women with FSAD without associated hypoactive sexual desire disorder (HSDD) (70% receiving androgen therapy). There was no evidence of efficacy in patients with FSAD in association with HSDD.

A number of aspects complicate the understanding of the dose-patient characteristics-response relationship in the

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clinical studies of sildenafil citrate in women with FSAD. These include:

- A strong placebo effect over time.
- Studies having different designs or duration.
- Studies being conducted in a mix of patient sub-populations.
- Different data collection instruments being used across studies to assess clinical endpoints.

The goal of this work was to develop a model-based quantitative framework to support drug development in FSAD. Telephone Sexual Activity Daily Diary (TSADD) data offer a good opportunity to study temporal aspects of clinical response under placebo and active treatment. Although the primary endpoint of all the studies was based on a validated sexual function questionnaire (SFQ), this was only administered at baseline and end of study (12 weeks). This modelling effort was therefore focused on the diary information that was captured every day across the whole time course of the study including the run-in phase.

This paper describes a model to characterize the probability of sexual events and their satisfaction scores over time. The impact of patient and disease characteristics were tested and incorporated in the model when appropriate. The model was qualified by using a posterior predictive check and was explored by simulating the expected dose-response in various patient populations to assess the impact of patient and disease characteristics on outcome.

MATERIALS AND METHODS

Data

Evaluable data were collected in 614 patients entered in three double-blind, placebo controlled studies: A1481123, A1481127 and A1481082 (noted here as 1123, 1127 and 1082, respectively). These studies were designed with a six-week treatment-free run-in followed by a 12-week treatment phase. The studies were conducted to evaluate the efficacy, safety and tolerability of oral sildenafil citrate in pre or postmenopausal women with FSAD without HSDD. The drug was to be taken approximately 1 h prior to anticipated sexual activity at either fixed (5, 10, 25, 50, 100 mg) or flexible (50 mg adjusted once to 25 or 100 mg depending on clinical response) doses. A summary of study characteristics is given in Table I. Median age was 43 years (range: 18 to 74 years). Subjects were required to have minimum physiological levels of both estradiol (plasma concentration greater than or equal to 40 pg/ml) and free testosterone (plasma concentration greater than or equal to 0.9 pg/ml) except in Study 1127 where patients were stratified according to testosterone levels. For all studies menopausal status was assessed as follows: naturally amenorrhoeic for more than one year, or a six-month history of amenorrhoea and a follicle stimulating hormone (FSH) level of >50 IU/l and serum estradiol <20 pg/ml, or bilateral oophorectomy. All patients provided written informed consent.

An interactive voice response telephone system was used where information for each day had to be entered whether or not the subject engaged in any sexual activity or took any drug. Subjects could enter more than one event per day. The main information collected was:

- whether the patient took part in a sexual event (yes, no), if yes the associated overall satisfaction rating using five categories from not satisfied: 1 up to extremely satisfied: 5,
- whether she experienced an orgasm (yes, no), if yes the associated orgasm satisfaction rating using five categories from not satisfied: 1 up to extremely satisfied: 5,
- whether the patient took the study drug (yes, no), if yes the time of drug intake in three categories (less than 30 min, 30 min to 4 h, more than 4 h before the sexual event).

In the current analysis an additional category: 0, was added to the orgasm score if no orgasm was reported. The structure of the data is described in Fig. 1.

Models

The model included two main components to account for the hierarchical structure of the TSADD clinical endpoint: a component for the time between sexual events and a component for orgasm and sexual satisfaction scores. Initial exploratory data analyses showed that 1) time between sexual events was independent of satisfaction score, and that 2) overall sexual satisfaction (S_{sex}) was strongly correlated with orgasm satisfaction (S_{org}). Therefore time-between-event and score models could be developed independently and overall sexual satisfaction was modeled as a function of orgasm satisfaction. The probability (p_{TS}) of observing a given level of satisfaction $S_{j,org}$ and $S_{j,sex}$ after time t of a patient j could be expressed as follows:

$$p_{TS}(t, S_{j,org}|z_j) = p_T(t|z_j)p_{S_{ORG}}(S_{j,org}|z_j, dose) \quad (1)$$

$$p_{TS}(t, S_{j,sex}|z_j) = p_T(t|z_j)p_{S_{SEX}|S_{ORG}}(S_{j,sex}|S_{j,org}, z_j) \quad (2)$$

where t is the time between sexual events in the jth patient, dose is sildenafil citrate dose and z_j denotes patient characteristics.

Time-Between-Event Model

The probability to have a sexual event $p_T(t|z_j)$ was modeled by a time to event model. In this model the dependent variable was the time between events t, and T^* denotes the time from previous event at which the next event occurs. We defined a hazard rate $h(t)$ and the probability for an event to occur after time t:

$$P(T^* \geq t) = \exp\left[-\int_0^t h(u)du\right] \quad (3)$$

The probability density function of event times t can be defined by

$$p_T(t) = h(t) \cdot P(T^* >= t) \quad (4)$$

Depending on the assumptions for the hazard rate, we can assume different structures of probability density func-

Table I. Summary of Studies

Study	1127	1082	1123
Phase	Phase 3	Phase 2b	Phase 2b
Patient number*	248	71 (early termination, 300 patients planned)	298
Design	Flexible dose	Fixed dose	Fixed dose
Doses (mg) (patient number or %)	Placebo (124), Active (124) Start on 50 mg, adjust to 25 mg (6%) or to 100 mg (75%)	Placebo (21), 5 (11), 10 (9), 25 (10), 50 (10), 100 (10)	Placebo (83), 5 (41), 10 (43), 25 (42), 50 (42), 100 (43)
Menopausal status (patient number)	Premenopausal (43) Postmenopausal on HRT (205)	Postmenopausal on HRT	Premenopausal
Estradiol	(≥40 pg/ml except for patients receiving HRT)	≥40 pg/ml	≥40 pg/ml
Free testosterone	Stratified: (≥0.9 pg/ml, 121 pts, or<0.9 pg/ml, 127 pts)	≥0.9 pg/ml)	≥0.9 pg/ml

HRT Hormone replacement therapy.
*Three women had no satisfaction data.

tion (pdf), $p_T(t)$. Here we assumed either a constant hazard, $h(t) = \lambda$ or a time-dependent hazard rate, $h(t) = \lambda \cdot p(\lambda \cdot t)^{p-1}$ which define exponential and Weibull distributions of t, respectively. The covariates z_j were tested in the models as predictors of the time between events with,

$$\lambda_j = \exp\left(\beta_1 + \beta_2 \cdot z_j + \eta_j\right)$$

Where β_1 and β_2 denote intercept and coefficient for covariate effects. The random effects η_j are independent individual random variables with a mean of zero and variance Ψ.

Satisfaction Score Model

Sexual satisfaction and orgasm satisfaction score were modeled simultaneously as ordered categorical variables using the logit transform $g(x)$ of the cumulative probability P that a score in an individual j is greater than n as follows:

$$g\left[P\left(S_{j,org} \geq n \middle| z_j, dose\right)\right] = \theta_n + f_{org}(z_j) + Pl_{org} + D_{org} + \eta_{j,org} \quad (5)$$

$$g\left[P\left(S_{j,sex} \geq m \middle| z_j, S_{j,org}\right)\right] = \theta_m + f_{sex}(z_j) + \theta_{cond} \times S^{\gamma}_{j,pred,org} + \eta_{j,sex} \quad (6)$$

with $g(x) = \ln\left[\frac{x}{1-x}\right]$

where θ_n and θ_m are the intercept of cumulative probabilities $n = 1, \ldots, 5$ for the orgasm satisfaction score and $m = 2, \ldots, 5$ for the sexual satisfaction score. Each cumulative probability was composed of a function of covariates ($f_{org}(z_j)$) and ($f_{sex}(z_j)$), placebo (Pl_{org}) and drug effect (D_{org}) components for orgasm satisfaction. Placebo effect was modelled as the effect of taking any pill and the drug effect was modelled as the effect of dose (conditional on taking a pill). The cumulative probability for sexual satisfaction is a function of the individual predicted orgasm satisfaction score ($S_{j,pred,org}$) and γ is a power parameter. The random effects η_j are independent individual random variables with a mean of zero and variance Ω.

The following covariate effects were assessed on models of the two scores independently: age, testosterone level, estradiol level, menopausal status, baseline scores, time from the last sexual event, and treatment duration.

Model Implementation

The Laplacian estimation method as implemented in the NONMEM program (version V) (9) was used to provide maximum likelihood estimates of the model parameters (see Appendix). Model selection was based on the log-likelihood ratio test (LRT). The difference in objective function (δ) (asymptotically x^2 distributed) was used to compare alternative models. All model comparisons were performed at the $p = 0.05$ level (difference of 3.8 for 1 degree of freedom).

Model Qualification

The models were independently qualified by posterior predictive check (10) for evaluating predictive performance. This involved Monte Carlo simulations of the original trials from which the models were derived. The covariance matrix of parameter standard error estimated by NONMEM was used as an approximation of posterior distribution of parameters (11). All parameters were drawn at each replicate from this matrix. We compared the range and median across 100 replicates of predicted responses (e.g., proportions $P(S_{org} \geq n)$, and $P(S_{sex} \geq m)$) and their 90% prediction intervals (taken

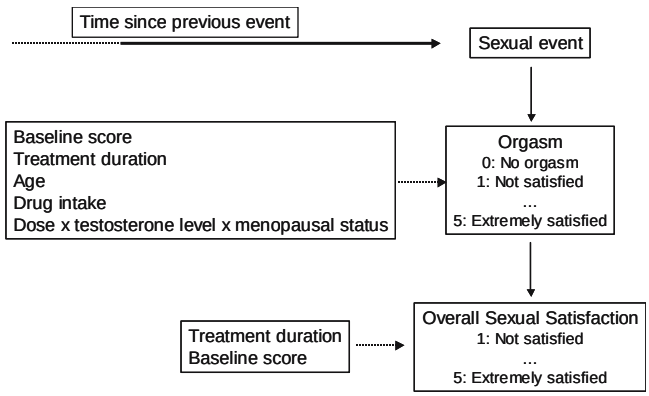

Fig. 1. Description of the data and model structure.

as the 5th–95th inter-percentile range), to those observed as a function of covariates and sildenafil citrate dose levels. The discrepancy between model and data were assessed graphically by the differences between the simulations and the observed data. These simulations were conditioned on observed patient characteristics and dosing histories. Of note, one study (1127) used a flexible adaptive design. The adaptiveness of the study design based on patient response was not taken into account.

Simulation Methods

Model simulations were undertaken to explore the expected clinical response as a function of relevant explanatory variables. At this stage only the probability of experiencing a satisfying orgasm, i.e., an orgasm satisfaction score of 3 or greater, $P(S_{org} \geq 3)$ as a clinical endpoint, has been evaluated. Simulations were integrated across uncertainty and interindividual variability in the model parameters and allowed to reflect 90% prediction intervals of the expected response. In these initial simulations, the expected response rate was simulated for a large group of patients (5,000). All simulations were performed using 12 weeks of treatment. Relevant patient covariates were sampled from the 1123, 1127 and 1082 study population.

RESULTS

Compliance to treatment was good. The proportion of drug intake before a sexual event was 80% and in 91% of the events, the drug was taken in the time window 30 min to 4 h before the sexual event. The proportion of drug intake was independent of treatment duration and dose.

A Weibull distribution best described the probability density function of the time between sexual events. Parameter estimates given in Table II indicated that the hazard of an event increased with time since the previous event. The modeling of covariates confirmed the independence between satisfaction scores and the time between events distribution. The strongest covariate effect was a small effect of treatment duration. Time between events increased slightly from 3.4 days during the first week to 3.7 days during the 12th week of treatment. Model qualification indicated good performance of the model (not shown).

The satisfaction scores were highly correlated in a contingency table of sexual scores *versus* orgasm scores and in the mosaic plot given in Fig. 2. Among the sexual events rated 1 (poorly satisfying, 13.2%), 93.6% were not associated with any orgasm ($S_{org} = 0$). Similarly, the vast majority (94.3%) of the 3.9% of sexual records rated 5, were associated with an orgasm rated 4 or 5.

The covariates were tested in both satisfaction score models independently. We selected age, treatment duration and baseline scores based on LRT. The model approach confirmed the independence of the sexual satisfaction score with the time between events as this covariate was not significant in improving model fit. The dependency on treatment duration was best described using an exponential function Eq. (7). This model assumes an increase of cumulative probabilities with time up to a plateau. Sexual satisfaction and orgasm satisfaction scores had very similar parameter estimates (time profiles).

Table II. Final Model Parameter Estimates

Parameter	Estimate	Standard error (CV %)	Description
TIME TO EVENT MODEL			
$\mathrm{Ln}(\lambda)$	− 1.410	1	Coefficient of the hazard model
$\mathrm{Ln}(p)$	0.316	4	Exponent of the hazard model
Ψ	0.125	7	Time to event model variance for random effect
ORDERED CATEGORICAL MODEL			
θ_1	− 0.428	55	Intercept for $P(S_{org} \geq 1)$
θ_2	− 0.521	45	Intercept for $P(S_{org} \geq 2)$
θ_3	− 1.240	19	Intercept for $P(S_{org} \geq 3)$
θ_4	− 2.760	9	Intercept for $P(S_{org} \geq 4)$
θ_5	− 5.140	5	Intercept for $P(S_{org} \geq 5)$
θ_6	− 2.270	14	Intercept for $P(S_{sex} \geq 2)$
θ_7	− 4.540	7	Intercept for $P(S_{sex} \geq 3)$
θ_8	− 6.880	5	Intercept for $P(S_{sex} \geq 4)$
θ_9	− 9.660	4	Intercept for $P(S_{sex} \geq 5)$
θ_{age}	− 0.035	13	Age effect
$\theta_{base,org}$	0.821	7	Baseline orgasm satisfaction effect
$\theta_{base,sex}$	1.460	9	Baseline sexual satisfaction effect
θ_{time}	0.338	17	Treatment duration effect
k (days^{-1})	0.096	29	Time exponent for treatment duration effect
θ_{pl}	1.01	9	Placebo effect
θ_{drug}	0.001	66	Drug x testosterone level effect
θ_{meno}	0.003	36	Increase in drug effect in post-menopausal patients
θ_{cond}	0.380	10	Link between overall sexual satisfaction and orgasm satisfaction
$\ln(\mathrm{SD}(\eta_{org}))$	0.272	14	Standard deviation for random effect for orgasm satisfaction
$\ln(\mathrm{SD}(\eta_{sex}))$	0.070	85	Standard deviation for random effect for sexual satisfaction

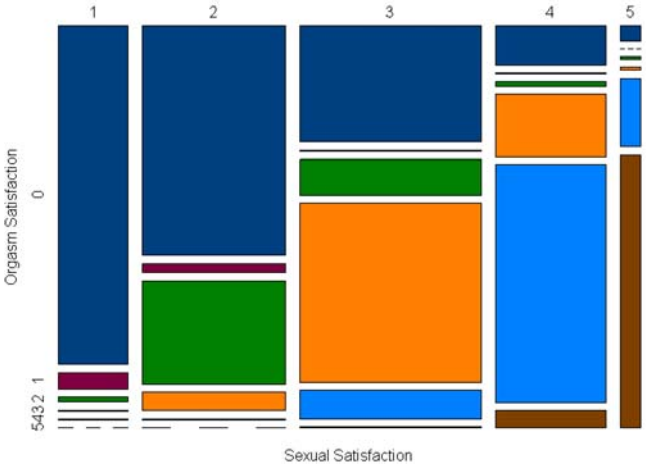

Fig. 2. Mosaic plot of contingency table for sexual satisfaction score (1–5) *versus* orgasm satisfaction score (0–5), width of column is proportional to the percentage of $S_{sex} = m$ and height is proportional to the percentage of $S_{org} = n$ (*left*) when $S_{sex} = m$ (*top*).

For the orgasm satisfaction score the final function of covariates was

$$f_{org}(z_j) = \theta_{base,org} \cdot base_{S_{org}} + \theta_{time} \cdot \left(1 - e^{-k \cdot time}\right) + \theta_{age,org} \cdot age \quad (7)$$

where $base_{S_{org}}$ is the baseline orgasm satisfaction scores, time is the time since start of the study, and age is in years, k is the time constant to reach the plateau and the regression parameters are specified by the relevant θ's. The same covariates were found to influence overall sexual satisfaction and orgasm satisfaction.

Sildenafil citrate doses and pill intake significantly improved the likelihood. An Emax model was tested but did not improve the fit. Finally the drug dose was conditioned on the pill intake in considering the product (dose · drgtaken) in the following model development, with drgtaken = 1 when the pill was taken (placebo or drug) before the event and 0 if not.

The interaction between dose effect and testosterone level was tested in implementing:

$$D_{org} = \theta_{drug} \cdot (dose \cdot drgtaken) + \theta_{tlevel} \cdot tlevel + \theta_{inter} \cdot (dose \cdot drgtaken) \cdot tlevel \quad (8)$$

where tlevel is the testosterone level in nanograms per milliliter. We compared this model to the additive model, $\theta_{inter} = 0$ and the reduced interaction $\theta_{tlevel} = 0$. Finally the latter was sufficient to describe the interaction. Other interactions between drug dose and menopausal status or baseline scores were tested but did not show significant improvement.

The placebo effect was described by the relationship

$$Pl_{org} = \theta_{pl} \cdot drgtaken \quad (9)$$

In adding the placebo effect to the drug component, we simplified the dose component interaction with:

$$D_{org} = \theta_{inter} \cdot (dose \cdot drgtaken) \cdot tlevel \quad (10)$$

To further evaluate the potential impact of menopausal status on the drug effect, the following model improved significantly the objective function (this interaction model was developed based on exploratory data analyses, not shown):

$$D_{org} = (\theta_{inter} + \theta_{meno} \cdot meno) \cdot (dose \cdot drgtaken) \cdot tlevel \quad (11)$$

Due to the conditional structure of the model it was not necessary to incorporate covariate effects in the sexual satisfaction model as such effects were accounted for in the predicted orgasm satisfaction. Based on similar parameter estimates obtained when the two scores were modeled independently, time effect parameters were assumed to be the same for the two scores to improve the precision of parameter estimates. The conditional structure of the two score was implemented by:

$$f_{sex}(z_j) = \theta_{base,sex} \cdot base_{S_{sex}} + \theta_{time} \cdot \left(1 - e^{-k \cdot time}\right) + \theta_{cond} \cdot S^2_{j,pred,org} \quad (12)$$

where $base_{S_{sex}}$ is the baseline sexual satisfaction score and $S^2_{j,pred,org}$ is the predicted orgasm score (see Appendix for more details). It should be noted that this predicted score is a transform of the categorical score to the continuous scale.

Parameter estimates are given in Table II. All parameters and particularly those related to covariate effects were well estimated. Covariate effects are summarized in Fig. 1. Drug effect is quite uncertain (CV of 66%) and this uncertainty is accounted for in the simulations given below. The estimate of the log standard deviation of interindividual variability for the sexual satisfaction score was poorly estimated (CV of 85%). In this model, orgasm satisfaction decreases in older patients, increases with baseline satisfaction, treatment duration (the estimated exponent, k, corresponds to a half life of 7.4 days consistent with the achievement of a plateau after about 3 to 4 weeks of treatment) and when a pill is taken (placebo effect). The drug effect is proportional to drug dose and testosterone level and stronger in postmenopausal patients (see model simulations). Overall sexual satisfaction is a function of the square (score exponent of 2) of orgasm satisfaction and it is also dependent on baseline satisfaction and subjected to the same treatment duration dependence as orgasm satisfaction. The exponent was fixed to 2 (based on preliminary estimates) to reduce the final parameterization of the model.

The score model was qualified by a posterior predictive check, the range and median across 100 replicates of predicted proportions $P(S_{org} \geq n)$, and $P(S_{sex} \geq m)$, to those observed as a function of treatment duration (not shown), age (not shown), baseline scores (not shown) and sildenafil citrate dose (shown in Fig. 3). Observed data were well within the 90th prediction interval of the simulation replicates. However, the predicted response after the lowest dose level (5 mg) was somewhat lower than expected.

According to model simulations, a fast onset of an increase of orgasm satisfaction after the start of treatment is expected. The probability of achieving a satisfactory orgasm: $P(S_{org} \geq 3)$ ranged (median, 90% prediction interval) from 34.7% (31.3–38.3%) for placebo to 41.6% (37.0–46.3%) for sildenafil citrate 100 mg. Thus the absolute treatment effect (difference from placebo) for sildenafil citrate was up to (median, 90% prediction interval) 6.9% (3.7–10%) for 100 mg

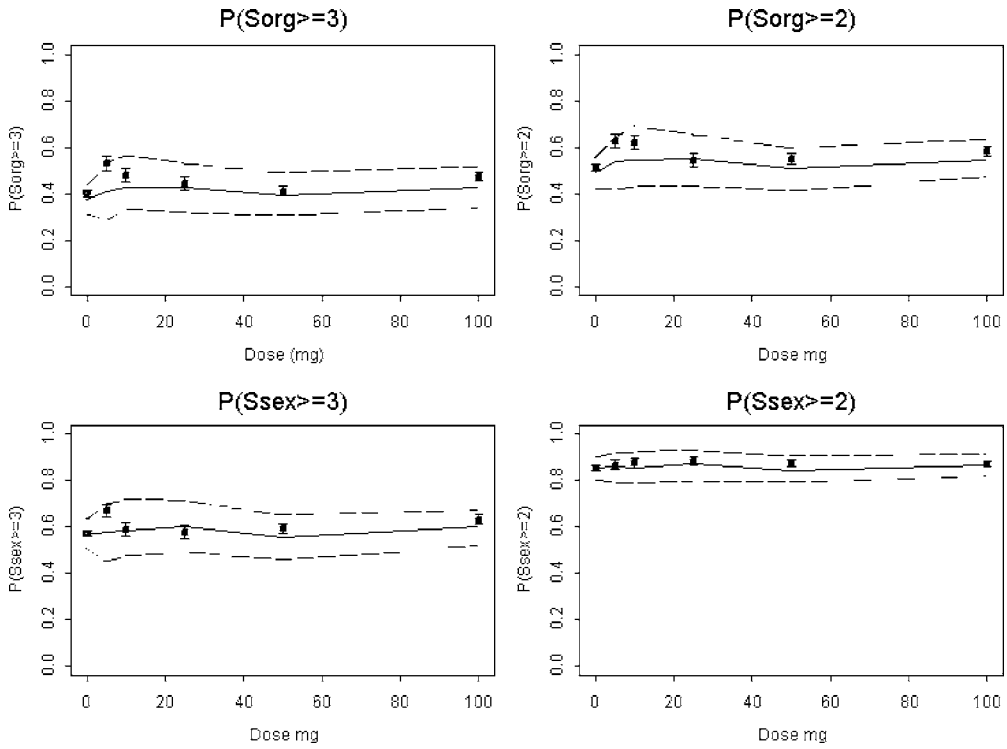

Fig. 3. Model qualification. Median (*dotted line*) and range (*hatched area*) of predicted proportions compared to observations (90% confidence interval) as a function of dose.

dose. The simulated dose-response curve is shown in Fig. 4. The treatment effect for sildenafil citrate was dependent on the testosterone level as measured at the start of the trial. The treatment effect of 100 mg sildenafil citrate ranged from 0.6 to 24.7% for testosterone levels of 0.1 to 4 pg/ml. In a patient population similar to that studied in the three analyzed trials, this should result in an average treatment effect for 100 mg sildenafil citrate varying from 4.2 to 11.5% for the lowest and the highest quartiles of the observed testosterone levels (Fig. 5). The treatment effect for sildenafil citrate in post-menopausal women was somewhat larger than in pre-menopausal women, despite the lower testosterone levels that are observed in the post-menopausal women. In addition, there was a substantial decline in orgasm satisfaction with age. However, the impact of age on treatment effect was minimal (Fig. 6).

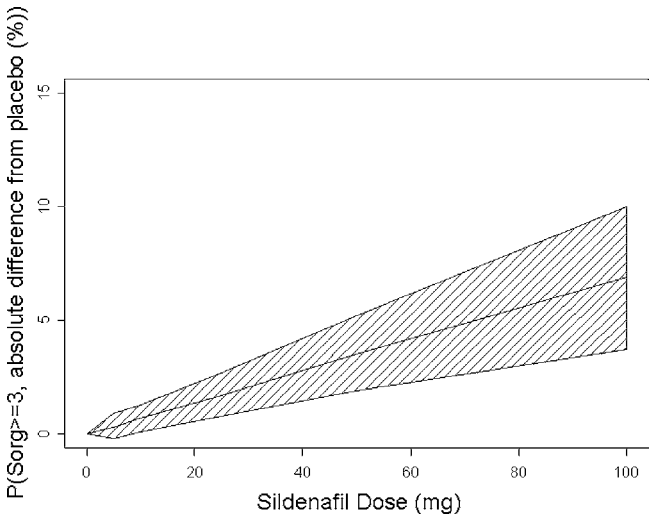

Fig. 4. Expected relationship between sildenafil dose and orgasm satisfaction score ($p(S_{org} \geq 3)$) in the FSAD patient population for the treatment effect of sildenafil (difference from placebo). The *solid line* represents the expected response and the *shaded area* represents the 90% prediction interval of the expected response.

DISCUSSION

We developed a model of longitudinal sexual activity daily diary data observed in three studies in 614 patients with FSAD. The model describes the probability distribution function of the time-between-sexual events and the joint distribution of orgasm satisfaction and overall sexual satisfaction for each of the sexual events. This work was seen as a learning exercise to provide a quantitative framework to support drug development in FSAD.

As expected, the hazard of engaging in a sexual event increased with time from the previous event (Weibull distribution). However, the expected time-between sexual events of 3.5 days showed only a marginal dependence on study duration and no dependence on baseline covariates or treatment.

This model-based analysis quantified the dose-response (on both sexual and orgasm satisfaction) of sildenafil citrate as a function of patient characteristics. Sildenafil citrate demonstrated a dose-dependent effect on the probability of orgasm and overall sexual satisfaction. A substantial drug effect was only observed, however, at the highest dose (100 mg) and in patients with high testosterone levels. Testosterone level markedly influenced treatment response consistent with the experimental observation of an up-regulation of nitric oxide synthase activity by testosterone (12). This limitation probably precluded two of the three studies (studies 1082 and 1123)

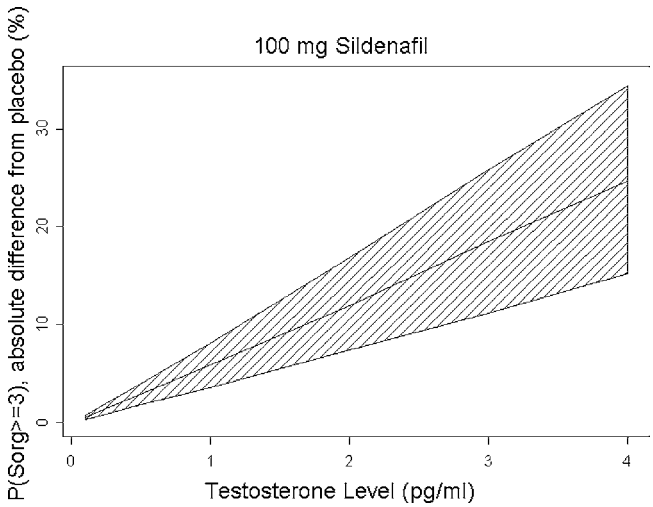

Fig. 5. Expected relationship between testosterone level at study entry and treatment effect of 100 mg sildenafil in the FSAD patient population (difference from placebo). The *solid line* represents the expected response and the *shaded area* represents the 90% prediction interval of the expected response.

being successful as the dose range studied (5 to 100 mg) was probably on the lower end of the dose-response curve. The greatest efficacy was observed in the flexible dose study (study 1127) where the starting dose of 50 mg was increased to 100 mg by 75% of the patients to achieve a better efficacy. However, the overall outcome in this study may have been negatively impacted as about half of the patients had low testosterone levels (below 0.6 pg/ml) and a substantial proportion (17%) of patients was premenopausal.

In addition this analysis quantified the placebo effect which is an important component of studies in patients with FSAD. The orgasm satisfaction rate increased from 27% (observed) at baseline to nearly 35% under placebo (an 8% increase). This effect is similar in magnitude to the drug effect (7% increase on top of placebo for 100 mg sildenafil citrate).

These characteristics might explain some of the inconsistencies seen in the outcome of sildenafil citrate studies in patients with FSAD.

Fig. 6. Expected relationship between age and orgasm satisfaction score ($P(S_{org} \geq 3)$, *left panel*) and treatment effect of 100 mg sildenafil (*right panel*). The *solid line* represents the expected treatment effect and the *shaded areas* represent the associated 90% prediction intervals.

Finally, we quantified the contribution of baseline covariates such as patient age and baseline sexual and orgasm satisfaction that influenced the response rate but not the treatment effect. The satisfaction score moderately increased with treatment duration to achieve a steady-state after only 3 to 4 weeks of treatment. It might therefore be unnecessary to conduct 12-week studies to show treatment effect in the future and longer studies are unlikely to alter outcome. For all three studies the SFQ changes (primary endpoint) from baseline to 12 weeks are consistent with diary data changes from baseline for the last 4 weeks of the studies. The FDA draft guidance on the clinical development of drug products for the treatment of female sexual dysfunction recommends the collection of diary data such that the endpoints studied should be based on the number of successful or satisfactory sexual events over time (13).

Although sildenafil citrate did not show sufficient efficacy to warrant further development in a broad patient population with FSAD, the current analysis provided an insight in the dose–patient characteristics-response relationship for this agent in women with FSAD. The model developed constitutes a useful tool to support future drug development in this and similar indications where sexual event diary data is collected.

Appendix

NONMEM CONTROL STREAMS

Time-to-event model

```
$PROB Weibull time to event
$INPUT ID TIME SSAT ORG ORGS AGE RAND TLE
   MENO DTK
STD DLT=DV BSS BOS MDV
; TIME DAYS
; SSAT satisfaction Score of current SEXUAL EVENT
; ORG orgasm 1 yes; 0 no
; ORGS orgasm satisfaction score
; AGE age in years
; RAND Sildenafil dose
; MENO menopausal status 0 = pre, 1 = post
; TLE testosterone level in ng/ml
; DTK pill intake 0 NO, 1 YES
; STD study
; DLT time since previous sex event
; BSS mean sex score at baseline
; BOS mean org score at baseline
$DATA ... IGNORE=i
$PRED
DT=DLT
IF(DT .EQ. 0) DT=.1
LABDA =EXP(THETA(1)+THETA(3)*TIME+THETA(4)
   *RAND+THETA(7)*DTK+ETA(1))
POW=EXP(THETA(2))
HAZ=LABDA*POW*(LABDA*DT)**(POW-1)
SURV=EXP(–(LABDA*DT)**POW)
DENS=SURV*HAZ
Y=DENS
$THETA
...
$OMEGA
$EST MAXEVALS=3000 PRINT=5 POSTHOC NOA-
   BORT METHOD=COND LAPLACE LIKE
$COV
```

Satisfaction score model

```
$PROB satisfaction score model FSAD treatment phase
   simultaneous fit
$INPUT ID TIME DV AGE RAND TLE MENO DTK
   STD BSS BOS MDV FLAG
; TIME days
; DV satisfaction Score of current sexual event
; AGE age in years
; RAND Sildenafil dose
; TLE testosterone level in ng/ml
; MENO menopausal status 0 = pre, 1 = post
; DTK pill intake 0 NO, 1 YES
; STD study
; BSS mean sex score at baseline
; BOS mean org score at baseline
; FLAG for DV 1: Orgasm 0: Sexual
$DATA ...IGNORE=i
$PRED
INT1=THETA(1)
INT2=THETA(2)
INT3=THETA(3)
INT4=THETA(4)
INT5=THETA(5)
FZ=E+THETA(14)*BOS+THETA(13)*AGE+THETA(11)
   *(1–EXP(–THETA(16)*TIME))
PL=THETA(15)*DTK
D=(THETA(12)+THETA(20)*MENO)*RAND*DTK*TLE
E=FZ+PL+D+EXP(THETA(18))*ETA(1)
A1=INT1+E
A2=INT2+E
A3=INT3+E
A4=INT4+E
A5=INT5+E
; Cumulative probabilities
P1=EXP(A1)/(1+EXP(A1))
P2=EXP(A2)/(1+EXP(A2))
P3=EXP(A3)/(1+EXP(A3))
P4=EXP(A4)/(1+EXP(A4))
P5=EXP(A5)/(1+EXP(A5))
; Probabilities
PR0=1–P1
PR1=P1–P2
PR2=P2–P3
PR3=P3–P4
PR4=P4–P5
PR5=P5
;Likelihood
IF(FLAG .EQ. 1 .AND. DV .GT. 4.5) Y=PR5
IF(FLAG .EQ. 1 .AND. DV .LE. 4.5 .AND. DV .GT. 3.5)
   THEN

   Y=PR4
```

```
ENDIF
IF(FLAG  .EQ. 1 .AND. DV .LE. 3.5 .AND. DV .GT. 2.5)
   THEN
   Y=PR3
ENDIF
IF(FLAG  .EQ. 1 .AND. DV .LE. 2.5 .AND. DV .GT. 1.5)
   THEN
   Y=PR2
ENDIF
IF(FLAG  .EQ. 1 .AND. DV .LE. 1.5 .AND. DV .GT. 0.5)
   THEN
   Y=PR1
ENDIF
IF(FLAG .EQ. 1 .AND. DV .LE. 0.5) THEN
   Y=PR0
ENDIF
; Predicted Sorg
IPRED=PR0*0+PR1+PR2*2+PR3*3+PR4*4+PR5*5
; SSAT conditionned on orgasm
INT6=THETA(6)
INT7=THETA(7)
INT8=THETA(8)
INT9=THETA(9)
E2 = THETA(10)* IPRED** 2 + THETA(17)* BSS+THETA
   (11)*(1–EXP(–THETA(16)*TIME))
E2=E2+EXP(THETA(19))*ETA(2)
A6=INT6+E2
A7=INT7+E2
A8=INT8+E2
A9=INT9+E2
; Cummulative probabilities
PS2=EXP(A6)/(1+EXP(A6))
PS3=EXP(A7)/(1+EXP(A7))
PS4=EXP(A8)/(1+EXP(A8))
PS5=EXP(A9)/(1+EXP(A9))
; Probabilities
PC1=1–PS2
PC2=PS2–PS3
PC3=PS–PS4
PC4=PS4–PS5
PC5=PS5
; Likelihood
IF(FLAG .EQ. 0 .AND. DV .GT. 4.5) Y=PC5
IF(FLAG  .EQ. 0 .AND. DV .LE. 4.5 .AND. DV .GT. 3.5)
   THEN
   Y=PC4
ENDIF
IF(FLAG  .EQ. 0 .AND. DV .LE. 3.5 .AND. DV .GT. 2.5)
   THEN
   Y=PC3
ENDIF
IF(FLAG  .EQ. 0 .AND. DV .LE. 2.5 .AND. DV .GT. 1.5)
   THEN
   Y=PC2
ENDIF
IF(FLAG  .EQ. 0 .AND. DV .LE. 1.5 .AND. DV .GT. 0.5)
   THEN
   Y=PC1
ENDIF
$THETA
...
$OMEGA 1 FIXED 1 FIXED
  $EST MAXEVALS=9000 PRINT=5 POSTHOC NOA-
BORT METHOD=COND LAPLACE LIKE
$COV
```

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