

# Modelling and Simulation of Telephone Sexual Activity Daily Diary Data of patients with female sexual arousal disorder treated with sildenafil (Viagra®)

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## Introduction

Sildenafil (Viagra®) is an orally active, selective inhibitor of cGMP specific phosphodiesterase type 5 (PDE5), approved for the treatment of male erectile dysfunction.

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.

Although some clinical studies in FSAD have shown statistically significant sildenafil efficacy over placebo others have not.

Three Phase 2b/3 studies had collected data in a consistent manner thus offering a good opportunity for a combined analysis to look at temporal aspects of clinical response under placebo and active treatment.

## Objectives

To develop models to:

- Characterize the probability of sexual events and their satisfaction scores over time based on Telephone Sexual Activity Daily Diary (TSADD) data obtained in clinical studies of sildenafil in patients with FSAD without concomitant Hypoactive Sexual Desire Disorder (HSDD).
- Simulate the expected dose-response in various patient populations to assess the impact of patient and disease characteristics on outcome.

## Data

Randomized, double blind, placebo controlled, multicenter studies to evaluate efficacy, safety and toleration of oral sildenafil administered for 12 weeks to women with FSAD

### Study 1127 - 248 women

- Pre-menopausal (n = 43) and postmenopausal (n = 205) women on HRT
- Minimum physiological level of estradiol ( $\geq 40$  pg/ml) except for patients on HRT
- Stratified according to free testosterone level ( $\geq 0.9$  pg/ml (n = 121) or  $<0.9$  pg/ml (n = 127))
- Dose: placebo (n = 124), 50 mg or adjusted doses (25 (6%) or 100 (75%) mg) (n = 124)

### Study 1082 - 71 women

- Postmenopausal on HRT with minimum physiological level of estradiol ( $\geq 40$  pg/ml) and free testosterone ( $\geq 0.9$  pg/ml)
- Dose: Placebo, 5, 10, 25, 50, 100 mg with 21, 11, 9, 10, 10, 10 patients respectively

### Study 1123 - 98 women

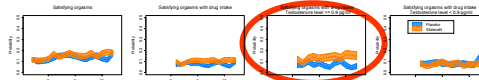
- Pre-menopausal with minimum physiological level of estradiol and free testosterone
- Dose: Placebo, 5, 10, 25, 50, 100 mg with 83, 41, 43, 42, 42, 43 patients respectively

All studies have 2-6 weeks treatment free and 12 wks treatment phase.

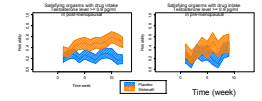
### Sexual Activity Daily Diary

- Captured every day
- Sexual events
  - Presence or absence
  - Satisfaction scale (1-5) (Ssex)
  - Event rated moderately to extremely satisfying (scale 3 to 5) were rated as satisfying
- Orgasm
  - Presence and absence
  - Satisfaction scale (1-5) (Sorg)
  - Satisfying events defined as above
- Time of drug intake before sexual event
  - Less than 30' minutes
  - 30' to 4 hours
  - Greater than 4 hours

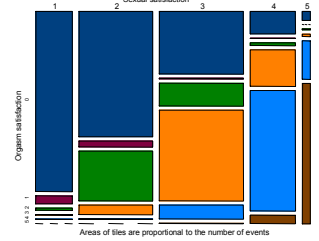
Study 1127  
Proportions of satisfying orgasms (Sorg $\geq 3$ ) versus time (90% confidence interval)



### ... by menopausal status

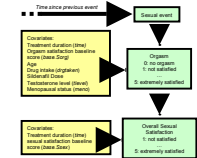


### Correlation of sexual satisfaction and orgasm satisfaction



## Model

The structure of the model was determined by the nature of the clinical endpoint that is derived from the TSADD



### Final Model

Time between events and scores are independent, time to event distribution was estimated by a Weibull distribution model in NONMEM

$$P(T \leq t) = 1 - \exp\left[-\int_0^t \lambda(t) dt\right] \text{ with } \lambda(t) \text{ with Weibull distribution } \lambda(t) = \lambda \cdot t^{\beta-1} \cdot e^{-\lambda t^\beta}$$

Orgasm and sexual satisfaction scores were modelled simultaneously in NONMEM

$$P(S_{sex} \geq s) = \exp\left[-\int_0^s \lambda_{sex}(t) dt\right] \text{ with } \lambda_{sex}(t) = \lambda_{sex} \cdot t^{\beta_{sex}-1} \cdot e^{-\lambda_{sex} t^{\beta_{sex}}}$$

$$P(S_{org} \geq s) = \exp\left[-\int_0^s \lambda_{org}(t) dt\right] \text{ with } \lambda_{org}(t) = \lambda_{org} \cdot t^{\beta_{org}-1} \cdot e^{-\lambda_{org} t^{\beta_{org}}}$$

$$E_{sex} = E_{org} \cdot \exp(\gamma \cdot \text{Time Since Last Orgasm}) \cdot \exp(\delta \cdot \text{Time Since Last Sexual Event}) \cdot \exp(\epsilon \cdot \text{Time Since Last Sildenafil Intake})$$

$$E_{org} = E_{sex} \cdot \exp(\eta \cdot \text{Time Since Last Orgasm}) \cdot \exp(\theta \cdot \text{Time Since Last Sexual Event}) \cdot \exp(\zeta \cdot \text{Time Since Last Sildenafil Intake})$$

$$\text{with } E_{sex} = \frac{1}{\Gamma(\beta_{sex})} \cdot \lambda_{sex}^{\beta_{sex}} \cdot t^{\beta_{sex}-1} \cdot e^{-\lambda_{sex} t^{\beta_{sex}}}$$

$$\text{and } E_{org} = \frac{1}{\Gamma(\beta_{org})} \cdot \lambda_{org}^{\beta_{org}} \cdot t^{\beta_{org}-1} \cdot e^{-\lambda_{org} t^{\beta_{org}}}$$

### Parameter estimates

Time to event model

Model	Estimate	90% CI	95% CI
lambda	0.0001	0.0001	0.0001
beta	1.000	1.000	1.000
gamma	0.000	0.000	0.000
delta	0.000	0.000	0.000
epsilon	0.000	0.000	0.000
eta	0.000	0.000	0.000
theta	0.000	0.000	0.000
zeta	0.000	0.000	0.000

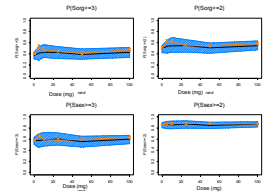
$$E(t) = \frac{1}{\Gamma(\beta)} \cdot \lambda \cdot t^{\beta-1} \cdot e^{-\lambda t^\beta}$$

where  $\Gamma$  is the Gamma function

Scores model

Parameter	Estimate	90% CI	95% CI
lambda_sex	0.0001	0.0001	0.0001
beta_sex	1.000	1.000	1.000
lambda_org	0.0001	0.0001	0.0001
beta_org	1.000	1.000	1.000
gamma	0.000	0.000	0.000
delta	0.000	0.000	0.000
epsilon	0.000	0.000	0.000
eta	0.000	0.000	0.000
theta	0.000	0.000	0.000
zeta	0.000	0.000	0.000

Posterior predictive check of  $P(\text{Sorg} \geq N)$  and  $P(\text{Ssex} \geq N)$  as a function of dose. We compared the 90% CI and median across 100 simulated replicates of predicted proportions to those observed

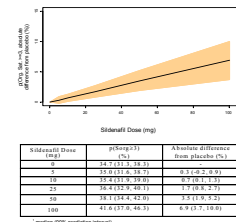


## Model Simulations

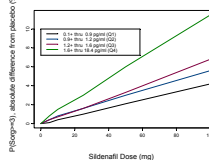
### Simulation of orgasm satisfaction score

- The probability of achieving a Orgasm Satisfaction Score,  $P(\text{Sorg}) \geq 3$  is used throughout the simulations.
- The response rate is evaluated for the expected patient population.
  - As such the performance of sildenafil in the expected patient population can be evaluated and is not affected by variability due to a limited trial size.
  - Subsequent trial simulations can then be performed to evaluate how this population performance can be translated into the performance of a trial (of limited size).
- Simulations are integrated across model uncertainty:
  - 500 replicates
  - 90% prediction intervals are represented
  - A population of 5,000 subjects is simulated for each replicate
  - Relevant patient covariates are sampled from the 1123/1127/1082 study population

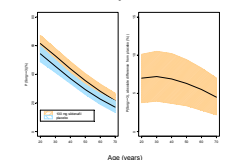
The expected absolute treatment effect for 100 mg Sildenafil may be 7%



Treatment responses for 100 mg Sildenafil may vary according to testosterone level from 4.0% (1st quartile) to 12% (4th quartile).



There is a substantial decline in orgasm satisfaction score with age. However, the impact of age on the treatment effect is minimal.



## Conclusions

- A model for the time-course of diary data observed in 3 Phase 2/3 studies of sildenafil was developed
- A Weibull distribution best described the probability density function of the time between sexual events
- Satisfaction scores were simultaneously modelled with overall sexual satisfaction conditional on orgasm satisfaction
- Simulations were performed to evaluate the expected clinical response in the FSAD patient population
  - $p(\text{Sorg} \geq 3)$  ranges from 34.7% for placebo to 41.6% for 100 mg sildenafil. Thus, the absolute treatment effect (difference from placebo) for sildenafil may be up to 6.9% for 100 mg sildenafil.
  - treatment effect of sildenafil is increased in post-menopausal women with high testosterone level.



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