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A two-part pilot study of sildenafil (VIAGRA™) in men with erectile dysfunction caused by spinal cord injury

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Study design: This was a two-part pilot study in men with erectile dysfunction (ED) due to spinal cord injury (SCI: cord level range T6-L5). Part I was a randomised, double-blind, two-way cross-over study comparing a single dose of sildenafil 50 mg or placebo. Part II was a randomised, double-blind, parallel-group evaluation of sildenafil 50 mg or placebo, taken as required (not more than once daily) approximately 1 h prior to sexual activity, over a period of 28 days.
Objectives: To assay the efficacy and safety of sildenafil 50 mg and placebo.
Setting: Clinic- and home-based assessments in the United Kingdom.
Methods: A total of 27 subjects who were able to achieve at least a grade 2 erection (hard, but not hard enough for penetration) in response to penile vibratory stimulation (PVS) were recruited. In Part I, the reflexogenic response of the penis to PVS was evaluated in the clinic while in Part II, the response to treatment was assessed in the home (global efficacy, questionniare, diary).
Results: In Part I, 17/26 (65%) subjects had erections of $>60\%$ rigidity at the penile base (median duration 3.5 min) after sildenafil compared with 2/26 (8%) (median duration 0 min) after placebo ($P=0.0003$). In Part II, 9/12 (75%) subjects on sildenafil and 1/14 (7%) subjects on placebo reported that the treatment had improved their erections ($P<0.005$), and 8/12 (67%) and 2/13 (15%) men, respectively, indicated that they wished to continue treatment ($P<0.02$). An analysis of diary data showed no difference between the groups with respect to the mean number of erections hard enough for penetration ($P=0.08$). The mean proportion of attempts at sexual intercourse that were successful was 30 and 15%, respectively ($P=0.21$). Similarly, responses to the end-of-treatment questionnaire indicated that there were no significant differences between the groups with respect to the frequency of erections hard enough for sexual intercourse ($P=0.47$) or that lasted as long as the subject would have liked ($P=0.11$). No subject discontinued sildenafil due to adverse events.
Conclusion: Sildenafil is an effective, well-tolerated oral treatment for ED in SCI subjects.
Sponsorship: This study was funded by Pfizer Inc.

Keywords: impotence; spinal cord injury; cyclic-GMP; phosphodiesterase inhibitors; sildenafil; erectile dysfunction; RigiScan

Introduction

Erectile dysfunction (ED), defined by the National Institutes of Health Consensus Panel as the inability to achieve or maintain an erection sufficient for satisfactory sexual performance,[1] is a common complication in men with a spinal cord injury (SCI). Approximately 10 000 traumatic SCIs are estimated to occur in the United States each year, with approximately two-thirds of these new cases involving individuals aged 16–30 years, of whom approximately 80% are men.[2]

The neurological level and severity of SCIs varies considerably, but in general more than half of all SCI men are unable to achieve erections that permit successful sexual intercourse.[3] Not surprisingly early and maximal attention to optimising the sexual function of men following a SCI has a high positive correlation with the overall success of rehabilitation.[4]

Corpus cavernosal smooth muscle relaxation and penile erection are predominately mediated by nitric oxide (NO) via the induction of cyclic guanosine monophosphate (cGMP) in the corpora.[5,6] It is hypothesised that an agent which acts to amplify the NO/cGMP signal in the corpus cavernosum would increase the intensity and duration of the erectile response to local tactile stimulation (mediated by the sacral reflex) in men with SCI.

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The orally active drug sildenafil acts peripherally as a selective inhibitor of cGMP-specific phosphodiesterase type 5,[7] an important regulator of cGMP in the human corpus cavernosum, and has been reported to significantly enhance the erectile response in able-bodied (non-SCI) men with ED of mixed and psychogenic aetiology.[8] This paper presents the results of a two-part, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of sildenafil (50 mg) for the treatment of ED in SCI subjects with some residual reflexogenic erectile capability.

Methods

Study design

This pilot study was conducted at three centres in the United Kingdom. A single triangular sequential trial design[9] (see Appendix I) was used so that subjects were not recruited unnecessarily. The study had two parts (Figure 1). Part I had a randomised, double-blind, two-way crossover design and assessed the reflexogenic erectile response to penile vibratory stimulation (PVS) after single doses of sildenafil or placebo; Part II was a randomised, double-blind, placebo-controlled, parallel-group evaluation of sildenafil in the home setting.

The protocol was approved by the Ethics Committee at each participating site. All patients in the study gave written informed consent.

Subjects

The entry criteria for the study were males aged 18–55 years, a documented history of SCI (sustained at least 6 months prior to screening), a female partner, ED solely attributable to SCI, and the ability to achieve at least a grade 2 reflexogenic erectile response (see *Assessments and statistical analyses*) to PVS (using FertiCare^{TM} vibrators) during screening.

Subjects receiving self-injection therapy for their ED were permitted to enter the study provided they met the above criteria and did not continue to use intracavernous injections in the week before screening or during the study. Subjects taking drugs with a recognised potential to be causally associated with ED were also eligible provided that the dose remained unchanged for 1 month before screening and throughout the study.

Subjects with SCIs at or above the T5 level were excluded to eliminate the potential risk of autonomic dysreflexia during PVS in Part I of the study. Subjects with genital anatomical deformities causing ED, or known or suspected vascular or endocrine causes of ED were also excluded from the study. Further exclusion criteria were known postural hypotension or a resting sitting blood pressure (BP) $<80/50$ mmHg, documented major haematological, renal or hepatic abnormalities, diabetes mellitus, and a history of stroke, subarachnoid haemorrhage, bleeding disorder or active peptic ulceration. Also excluded from entry were subjects receiving nitrates or anticoagulants, men who had taken any experimental drug within the previous 3 months, and subjects who drank more than 28 units of alcohol per week (1 unit = 1/2 pint of beer, 0.8 ounce of spirits, or 1 glass of wine). Subjects who were clinically depressed were excluded unless the investigator could ensure that they had the motivation to participate reliably in the study.

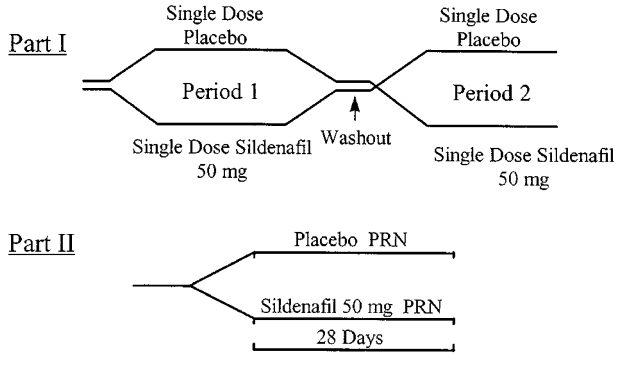

Figure 1 Study design

Drug treatment

In Part I, men were assigned to receive single doses of sildenafil 50 mg (2×25 mg capsules) and matching placebo in a random order, with a washout period of at least 3 days between treatment periods; this was based on the half-life of sildenafil (approximately 4 h).[10] In Part II, subjects were randomised to either sildenafil 50 mg or placebo for 28 days. As the observed time to maximum plasma concentration (T_{max}) of sildenafil is approximately 60 min,[10] subjects were instructed to take their treatment as needed approximately 1 h prior to sexual activity, but not more than once daily.

Assessments and statistical analyses

In Part I, the duration of erections of $>60\%$ and $>80\%$ rigidity (an erection $>60\%$ rigidity is considered as sufficient for penetration[7,8]) at the base and tip of the penis in response to PVS were recorded 30, 60 and 90 min after drug dosing using penile plethysmography (RigiScan Plus^{TM}); the vibrator settings used in both cross-over periods were those which had maximised the reflexogenic erectile response during screening. Sitting BP and pulse rate measurements were performed throughout penile plethysmography and any subject showing a hypertensive dysreflexic response was immediately withdrawn from the study. A subjective assessment of the best reflexogenic erectile response was also recorded by the patient using a five-point qualitative scale (0 = no response, 1 = increase in size, but not hard, 2 = hard,

but not hard enough for penetration, 3 = hard enough for penetration, but not completely hard, 4 = completely hard).

At the end of Part II, subjects were asked two global efficacy questions: '*Has the treatment you have been taking recently* (*over the last 4 weeks*) *improved your erections*?' (Question A) and '*If this treatment you have been taking recently were freely available would you want to continue taking it*?' (Question B).

Subjects also completed a diary during Part II, recording information on drug dosing, and quality of all erections associated with sexual stimulation, stating hardness and whether erections lasted long enough for satisfactory sexual activity. Subjects also answered an eight-item sexual function questionnaire and their partners were simultaneously asked to complete a two-item questionnaire (for full details of both see Appendix II) at the screening visit and after 28 days of treatment. The responses to both questionnaires were scored using a five-point scale, in which a score of one was the least favourable.

All adverse events that occurred during study treatment or within 7 days of the end of treatment were recorded, regardless of causality, and were graded by severity (mild, moderate, severe). Routine biochemical and haematological safety tests were also performed at the screening visit, during the 28-day treatment period and at a follow-up visit 2 weeks later.

The primary efficacy variable was the response to global efficacy question A. The secondary efficacy variables were the responses to global efficacy question B, the patient sexual function and partner questionnaires, the weekly count of erections sufficient to permit intercourse (grades 3 or 4), and the proportion of attempts at sexual intercourse that were successful (defined as occasions when the subject took the study drug, had a grade 3 or 4 erection, and stated that the erection lasted long enough for satisfactory sexual activity).

Intent-to-treat (ITT) analyses were performed for all the efficacy variables. The ITT analyses included all randomised subjects who received treatment and had any post-baseline assessments, regardless of any protocol deviations or whether they completed the study. All significance tests were two-sided and tested at the 5% level; details of the specific statistical tests used are presented in Appendix I.

Results

Recruitment and demographic characteristics

A total of 27 subjects were randomised before recruitment to the study was closed (see Appendix I). The two randomised groups in Part II [sildenafil (13), placebo (14)] were comparable in terms of age, duration of ED and the degree of spinal cord lesion assessed on the criteria of the American Spinal Injury Association (ASIA) Impairment Scale[11] (see Table 1). One subject randomised to the sildenafil group was lost to follow-up before completing Part I and is therefore not included in the analysis of results.

The median duration of treatment in both groups during Part II was 33 days, with subjects taking a median of eight doses of either sildenafil or placebo. Overall, 13 subjects (48%) had received previous drug or non-drug treatment(s) for ED. Concomitant medications were taken by 21 subjects during the study, with similar numbers in each of the treatment groups.

Table 1 Demographic data for the randomised subjects

	Randomised drug for Part II	
Characteristic	*Sildenafil* (n = 13)†	*Placebo* (n = 14)††
Mean age, year (range)	32 (21–49)	34 (22–47)
Mean duration of ED, year (range)	6.7 (0.8–24.0)	7.8 (1.0–23.0)
Degree of spinal cord lesion*		
A (complete)	8†	6
B (incomplete)	2	1
C (incomplete)	2	3
D (incomplete)	1	4
E (normal)	0	0

ED = erectile dysfunction. *American Spinal Injury Association Impairment Scale categories, where A = complete (no sensory or motor function preserved in the sacral segments S4-S5); B = incomplete (partial sensory function but no motor function is preserved below the neurological level and extends through the sacral segments S4-S5); C = incomplete (motor function is partially preserved below the neurological level, and the majority of key muscles below the neurological level have muscle grade $<3/5$); D = incomplete (motor function is preserved below the neurological level, and the majority of key muscles below the neurological level have muscle grade $\geqslant 3/5$); and E = normal (sensory and motor function normal).[11] †One subject was lost to follow-up during Part I of the study. ††One subject was non-evaluable in Part II as there was no evidence that medication had been taken

Efficacy

In Part I of the study, 17 of the 26 subjects (65%) had erections >60% rigidity at the penile base after sildenafil treatment compared with two (8%) after placebo ($P<0.01$; Figure 2). The median duration of the erections achieved was 3.5 and 0.0 min, respectively; the estimated median treatment difference was 5.5 min [95% confidence interval (CI) 2.0–15.25; $P=0.0003$]. A total of nine (35%) subjects had erections >80% rigidity at the base of the penis after sildenafil compared with one (4%) after placebo, and the estimated median difference between the treatments for the duration of the erection was 0.25 min (95% CI 0–2.25; $P=0.01$).

For penile tip recordings, 12 men (46%) had erections >60% rigidity on sildenafil, compared with one (4%) after treatment with placebo (Figure 2). Corresponding figures for penile tip recordings >80% rigidity were six (23%) and none (0%), respectively. The estimated treatment differences in duration of erections >60% and >80% rigidity were 1.25 min (95% CI 0–5; $P=0.0016$) and 0 min (95% CI 0–0.75; $P=0.0166$), respectively.

Data on the mean subjective grade of erection achieved after PVS in Part I is presented in Figure 3; the difference of 1.16 (95% CI 0.69–1.61) in mean grade between sildenafil and placebo was highly significant ($P<0.0001$).

In response to global efficacy question A at the end of Part II of the study, 9/12 (75%) subjects in the sildenafil group and 1/14 (7%) subjects in the placebo group stated that treatment had improved their erections ($P<0.005$) (Table 2). In the sildenafil group, an improvement in erections was reported by all five (100%) of the subjects with incomplete spinal cord lesions (ASIA grade B–D) and four of the seven subjects (57%) with complete cord lesions (ASIA grade A). In response to global efficacy question B, 67% of the sildenafil group and 15% of the placebo group indicated that they would want to continue treatment if it were available at the end of the study ($P<0.02$; Table 2).

The analysis of diary data indicated that the mean number of erections hard enough for penetration was 1.8/week for subjects receiving sildenafil compared with 0.4/week for those receiving placebo ($P=0.08$). The mean proportion of attempts at sexual intercourse that were successful was 30 and 15%, respectively; this difference was not statistically significant ($P=0.21$).

Of the seven questions analyzed from the patient sexual function questionnaire, only the mean response scores for the question assessing satisfaction with sex life (question 7) demonstrated a statistically significant difference ($P=0.01$) between treatment groups, with subjects in the sildenafil group being more satisfied with their sex life (Table 2). Although not reaching statistical significance, mean response scores for the questions assessing the frequency and quality of erections (questions 4, 5 and 6) were higher for sildenafil-treated subjects than for those treated with placebo (Table 2). The mean response scores for the two questions on the partner questionnaire were also higher for the sildenafil than the placebo group, although these differences did not attain statistical significance (Table 2).

Safety

All 27 subjects were included in the safety analyses and the results are reported in Table 3. During Part I, when single doses were administered, seven (26%) subjects experienced a total of nine events after sildenafil, and

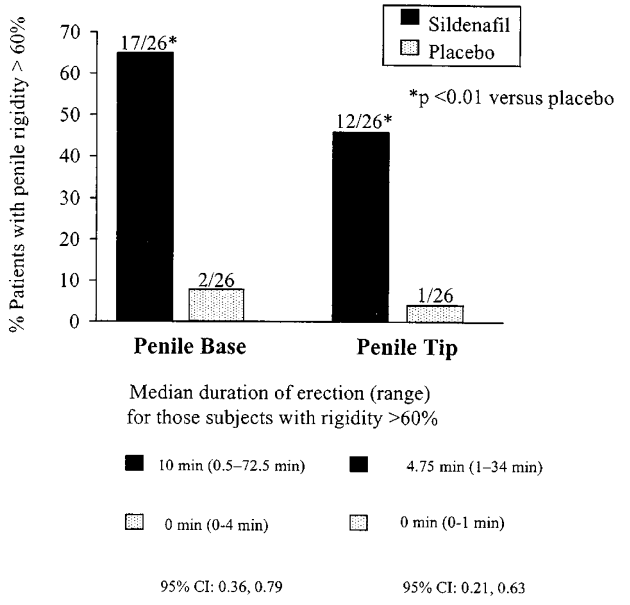

Figure 2 The percentage of subjects with penile rigidity >60% including median duration in minutes as measured by penile plethysmography (Part I)

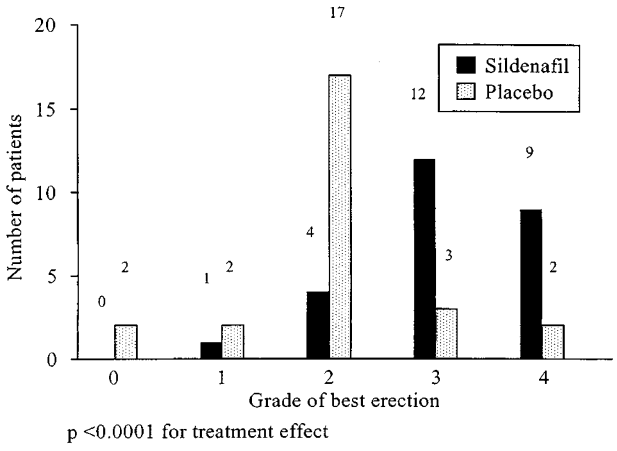

Figure 3 Subject assessment of rigidity of best erection achieved during PVS (Part I)

Table 2 Efficacy outcomes in Part II

	Sildenafil ($n=12$)	*Placebo* ($n=14$)	*95% CI*	P *value*
Subjects indicating improvement in erections (global efficacy question A)	9 (75%)	1 (7.1%)	0.50, 0.86	0.004
Subjects who would want to continue treatment (global efficacy question B)	8 (66.7%)	2 (15.4%)*	0.35, 0.70	0.018
Frequency of erections when sexually stimulated (mean ± SEM) (patient question 4)	3.68 ± 0.59	2.57 ± 0.74**	−0.73, 2.95	0.25
Frequency of erections hard enough for intercourse (mean ± SEM) (patient question 5)	2.75 ± 0.56	2.13 ± 0.68**	−1.10, 2.34	0.47
Erections lasting long enough (mean ± SEM) (patient question 6)	2.71 ± 0.51	1.49 ± 0.61**	−0.33, 2.77	0.11
Subject's satisfaction with sex life (mean ± SEM) (patient question 7)	3.72 ± 0.37	2.20 ± 0.40*	0.45, 2.59	0.01
Quality of patner's erections (mean ± SEM) (partner question 1)	3.78 ± 0.45†	2.84 ± 0.50††	−0.38, 2.26	0.16
Quality of sex life (mean ± SEM) (partner question 2)	3.36 ± 0.37†	2.84 ± 0.41††	−0.56, 1.60	0.32

*$n=13$; **$n=11$; †$n=10$; ††$n=9$. 95% CI = 95% confidence intervals. Maximum score for patient questions 4–7 and partner questions = 5

Table 3 Reported adverse events during Parts I and II

	Sildenafil	*Placebo*
Headache	4	1
Dyspepsia	1	0
Rash	2	3
Anxiety	1	0
Dizziness	1	0
Vomiting	1	0
Rectal disorder	1	0
Respiratory tract infection/disorder	4	2
Increase in cough	0	1
Asthenia	0	1
Malaise	0	1
Flu syndrome	0	1
Epididymitis	0	1
Orchitis	0	1
Total events	15	12

four (15%) subjects reported four events after placebo administration. During Part II, five (42%) men in the sildenafil group and four (31%) men in the placebo group reported six and eight adverse events, respectively. Of the 15 reported events with sildenafil, only four (anxiety and headache in Part I, dyspepsia and a respiratory disorder in Part II) were considered by the blinded investigator to be treatment related. There were no serious events associated with sildenafil, but one subject in the placebo group in Part II was hospitalised due to severe epididymitis and orchitis.

Sildenafil had no effect on the sitting BP or pulse rate during Part I. One subject randomised to the sildenafil group in Part II had a laboratory test abnormality (elevated neutrophil count) during the study, but this was not considered to be treatment-related and did not result in study withdrawal.

Discussion

Sildenafil acts to amplify the effects of the NO/cGMP pathway in the penis during sexual stimulation. It should therefore require at least partial integrity of the neural pathway mediating erection in order to exert a therapeutic effect. In men with SCI, sildenafil may increase the erectile response to local tactile stimulation (via the sacral reflex) or to psychogenic stimuli depending upon which pathways may still be preserved.

In Part I of this study, sildenafil was shown to significantly improve reflexogenic erectile responses to PVS. Penile plethysmography showed that 65% of subjects had satisfactory erections of >60% rigidity at the penile base (median duration of 3.5 min) after sildenafil compared with 8% following placebo (median duration 0 min) ($P=0.0003$). This objective parameter of erectile function agreed well with the reports of grade 3 or 4 erections in the home setting, as some 70% of subjects who had satisfactory erections and no response on placebo also had grade 3 or 4 erections when radomised to receive sildenafil in Part II. These results suggest that for this study population a therapeutic threshold of penile basal rigidity of >60% is a fair and conservative indicator of erections rigid enough for penetration (grade 3 or 4) during sexual intercourse.

Subjects receiving sildenafil during Part II reported that treatment had significantly improved their erections ($P<0.05$) and satisfaction with their sex life ($P=0.01$). Furthermore, significantly more men in the sildenafil group than in the placebo group (67% *vs* 15%) wanted to continue treatment at the conclusion of the study ($P<0.02$).

In contrast, the results of other secondary efficacy variables in the sexual function questionnaire, the

partner questionnaire and diary data, although favouring sildenafil, failed to attain statistical significance. This lack of significance in these secondary endpoints is a not entirely unexpected consequence of using a sequential analysis technique, which in this study led to early termination of recruitment because of the clear treatment-related difference arising for the primary efficacy endpoint. The latter variable only assessed patients self-reported improvement in erectile function during sexual activity.

Sildenafil treatment was well tolerated with no withdrawals due to study drug intolerance. All subjects in the sildenafil treatment group completed the 28-day study, with the exception of one who was lost to follow-up. During this part of the study only two subjects in the sildenafil group experienced adverse events (dyspepsia and chest infection) that were judged to be treatment-related. Adverse events in both parts of the study were predominantly mild in severity. No clinically significant drug-related change in a laboratory test measurement was found during the study. These findings are consistent with those of previous studies with sildenafil, in which the main adverse events were headache, vasodilation and dyspepsia.[8]

The majority of our subjects received at least one concomitant medication during the study and there was no evidence of any adverse drug interactions between these drugs and sildenafil. Indeed, few clinically important drug interactions have been identified with sildenafil during the phase III trial programme or in the several interaction studies that have been conducted in healthy volunteers. However, sildenafil and nitrates share a common metabolic pathway and should not be co-administered. While no significant interaction has been demonstrated between sildenafil and oral anticoagulants or antiplatelet agents, it is recommended that sildenafil is administered with caution to patients with bleeding disorders or active peptic ulceration. Sildenafil is hepatically metabolised by cytochrome 3A4 and clearance is reduced when co-administered with inhibitors of this enzyme, such as cimetidine. Although sildenafil exerts mild vasodilatory effects, it can also be safely administered to patients receiving antihypertensive therapy.[12]

Following the success of this pilot study, which has demonstrated the capability of treating ED in SCI men with a simple-to-take oral medication that exerts its effect only with sexual stimulation, a two-way cross-over, double-blind, placebo-controlled, 6 week study is now underway. This trial will investigate flexible dosing with up to 100 mg of sildenafil taken 1 h before sexual activity in a larger population of subjects recruited from European SCI units.

In conclusion, oral sildenafil taken not more than once daily is well tolerated and significantly improves the quality of erections and satisfaction with sex life in men with ED caused by a SCI. The peripheral site of action of sildenafil affords the opportunity to amplify reflexogenic erectile responses and increase the opportunity for a more appropriate and natural response during sexual activity in SCI men.

References

1 NIH Consensus Development Panel on Impotence. Impotence. *JAMA* 1993; **270:** 83–90.
2 Spinal Cord Injury: Facts and Figures at a Glance. Information Sheet. National Spinal Cord Injury Statistical Center; Birmingham, AL: July 1996.
3 Bors E, Comarr AE. Neurological disturbances of sexual function with special reference to 529 subjects with spinal cord injury. *Urol Surv* 1960; **10:** 191–222.
4 Biering-Sørensen F, Sønksen J. Penile erection in men with spinal cord or cauda equina lesions. *Semin Neurol* 1992; **12:** 98–105.
5 Andersson K-E, Wagner G. Physiology of penile erection. *Physiol Rev* 1995; **75:** 191–236.
6 Burnett AL. The role of nitric oxide in the physiology of erection. *Biol Reprod* 1995; **52:** 485–489.
7 Boolell M *et al*. Sildenafil: an orally active type 5 cyclic GMP-specific phosphodiesterase inhibitor for the treatment of penile erectile dysfunction. *Int J Impotence Res* 1996; **8:** 47–52.
8 Boolell M, Gepi-Attee S, Gingell JC, Allen MJ. Sildenafil, a novel effective oral therapy for male erectile dysfunction. *Br J Urol* 1996; **78:** 257–261.
9 Whitehead J. The Design and Analysis of Sequential Clinical Trials. 2nd edn. Ellis Horwood: Chichester, 1992.
10 Muirhead GJ *et al*. Pharmacokinetics of sildenafil (VIAGRA™), a selective cGMP PDE5 inhibitor, after single oral doses in fasted and fed healthy volunteers. *Br J Pharmacol* 1996; **42:** 268P.
11 Ditunno JF, Young W, Donovan WH, Creasey G. The International Standards Booklet for Neurological and Functional Classification of Spinal-cord Injury. *Paraplegia* 1994; **32:** 70–80.
12 Morales A *et al*. Clinical safety or oral sildenafil citrate (VIAGRA™) in the treatment of erectile dysfunction. *Int J Impotence Res* 1998; **10:** 69–74.

Appendix I

Study design and statistical methods

Study design
As the recruitment of men with ED due to SCI was anticipated to be difficult, and because there has been no previous study of the efficacy of sildenafil in this population, this study used a single triangular sequential design[9] in which recruitment could be stopped as soon as a statistical difference between sildenafil and placebo was demonstrated. The decision to continue or terminate recruitment was made by an independent data monitoring committee based on specific interim sequential analyses of the response to the global efficacy question A ['*Has the treatment you have been taking recently* (*over the last 4 weeks*) *improved your erections*?'] at the end of Part II of the study.

The first interim analysis was conducted after the initial 12 individuals had completed both parts of the study and further interim analyses were then performed after every four additional subjects completed. The assumed response rate for the sample size

calculations was 60% in the sildenafil group and 25% in the placebo group. Based on this methodology the sample size was unknown prior to the start of the study; however, the expected number of subjects that was calculated was 39, with a maximum of 88.

A significant difference between the treatment groups in the response to global efficacy question A was seen after the third interim analysis, ie when 20 subjects had completed the study. However, at this time, an additional seven subjects had already been randomised to the study, six of whom had not yet completed and these subjects were allowed to continue.

Statistical methods

In Part I, the duration of erections $>60\%$ and $>80\%$ rigidity at the base and tip of the penis (four separate endpoints) were analyzed using non-parametric analysis as the data were highly skewed. For subjects who had more than one erection, the sum of the durations over the 90-min assessment period was calculated. The patient assessment of the best erectile response to PVS during each cross-over period was assessed using analysis of covariance (ANCOVA) appropriate for a cross-over design.

In Part II, the responses to global efficacy questions A and B were analyzed using logistic regression, including terms for treatment and centre effect. The proportion of successful attempts at sexual intercourse were analyzed using the non-parametric Cochran-Mantel-Haenszel test of association, adjusted for centre effect. The weekly count of grade 3 or 4 erections from the diary and the responses to the patient sexual function and partner questionnaires were analyzed using ANCOVA, including terms for treatment, baseline effect (patient sexual function and partner questionnaires only), and centre effect. Both the ANCOVA and logistic analyses included the demographic covariates of age, smoking status, time since SCI, and site of lesion.

Appendix II

Sexual function questionnaires

Patient questionnaire:

(1) Over the past 4 weeks on how many days have you felt sexual desire?
(2) Over the past 4 weeks how would you rate your level of sexual desire?
(3) Over the past 4 weeks how frequently did you wake from sleep with a partial or full erection?
(4) Over the past 4 weeks how often have you had full or partial erections when you were sexually stimulated in any way? (Sexual stimulation includes situations such as loveplay with a partner).
(5) Over the past 4 weeks, when you had erections, how often would you say they were hard enough to have sex?
(6) Over the past 4 weeks when you have had erections that you wanted (eg for intercourse or masturbation) how often did the erection last as long as you would have liked?
(7) Over the past 4 weeks how satisfied have you been with your sex life?
(8) Over the past 4 weeks have you used any devices (such as vibrators) in sexual activity with your partner?

The answer to question 8 was only designed to detect whether subjects started to use (or changed the frequency of use of) vibrators after exposure to such devices in Part I of the study, and was not included in the efficacy analysis.

Partner questionnaire:

At screening:
(1) Over the past 4 weeks to what extent do you consider your partner's ability to get and keep erections to be a problem?
(2) Over the past 4 weeks how have you felt about your sex life with your partner?

At the end of Part II:
(1) On average, how has the quality of your partner's erections changed over the period he was taking the trial medication?
(2) Overall, how has the quality of your sex life changed since your partner started taking new trial medication?