An open-label, long-term evaluation of the safety, efficacy and tolerability of avanafil in male patients with mild to severe erectile dysfunction

L. H. Belkoff,1 A. McCullough,2 I. Goldstein,3 L. Jones,4 C. H. Bowden,5 K. DiDonato,5 B. Trask,5 W. W. Day5

SUMMARY

Aim: Determine the long-term efficacy, safety and tolerability of avanafil, a highly specific, rapidly absorbed phosphodiesterase type 5 inhibitor in male patients with mild to severe erectile dysfunction (ED), with or without diabetes. Methods: This was a 52-week, open-label extension of two 12-week, randomised, placebo-controlled, phase 3 trials. Patients were assigned to avanafil 100 mg, but could request 200 mg (for increased efficacy; ‘100/200-mg’ group) or 50 mg (for improved tolerability). Primary end points included percentage of sexual attempts ending in successful vaginal penetration (Sexual Encounter Profile 2 (SEF2)) and intercourse (SEP3) and erectile function domain score per the International Index of Erectile Function (IIEF-EF). Results: Some 712 patients enrolled; 686 were included in the intent to treat population and contributed to the data. All primary end points showed sustained improvement. SEP2 and SEP3 success rates improved from 44% to 83% and from 13% to 68% (100-mg group) and from 43% to 79% (200-mg group). Avanafil was effective in some patients ≤ 15 min and > 6 h postdose. Sixty-five per cent (112/172) of ‘nonresponders’ to avanafil 100 mg responded to the 200-mg dose. The most common (≥ 2%) treatment-emergent adverse events were headache, flushing, nasopharyngitis and nasal congestion; < 3% of patients discontinued therapy because of adverse events. Conclusions: The long-term tolerability and improvement in sexual function, coupled with rapid onset, suggest that avanafil is well suited for the on-demand treatment of ED.

What’s known
• Phosphodiesterase type 5 (PDE5) inhibitors are the standard of care for erectile dysfunction.
• Administration is generally recommended 30–120 min before sexual activity, and efficacy rates for available agents range from 52% to 66% at their highest doses.
• Potential adverse events of particular concern with this drug class include visual disturbances and haemodynamic changes, possibly because of cross-reactivity with other PDEs.

What’s new
• Avanafil has an onset of action as early as 15 min in some patients.
• Efficacy (successful intercourse; Sexual Encounter Profile question 3) is > 65% with the 100-mg and 200-mg doses.
• Long-term data indicate that avanafil is well tolerated, with low incidence rates of adverse events.

Introduction

In the United States, it is estimated that erectile dysfunction (ED) affects more than 18 million males, a figure that represents 18.4% of the male population 20 years of age or older (1). ED is associated with advanced age (2,3); the Massachusetts Male Aging Study determined that 52% of males aged 40–70 years experience some degree of ED, with the incidence increasing progressively with age (2).

In addition to age, medical conditions, such as cardiovascular disease and diabetes mellitus, are associated with ED (1). In a cross-sectional analysis of data (N = 2126) from the 2001–2002 National Health and Nutrition Examination Survey (NHANES), approximately half of all males with a history of heart disease or with diabetes also had ED. Multivariate analysis of the NHANES data further indicated that ED was significantly and independently associated with diabetes (1).

The evolving understanding of ED has led to focused efforts to develop effective treatments, most notably, the commonly prescribed phosphodiesterase type 5 inhibitors (PDE5is) (4). Several factors, including clinical presentation, patient demographic and personal situation, may influence the choice of a PDE5i (5), and data from a large longitudinal community-based study from the Netherlands (the Krimp study) suggested that the availability and awareness of new treatment options (i.e. PDE5is) for ED induced a change of behaviour in general practitioners and their patients, regarding treatment-seek-
ing and procurement (6). For the achievement of successful intercourse, PDE5is that have been prescribed for more than a decade have demonstrated favourable efficacy (7), ranging from 52% to 66% at their highest doses (8–10). The timing of administration for these agents is approximately 30–120 min prior to anticipated sexual activity, with effects lasting 4–36 h (4,8–11).

Although efficacy has been demonstrated with commonly prescribed PDE5is, adverse events (AEs) have been observed with this drug class. Visual disturbances, including rare vision loss (transient or permanent) and impaired colour discrimination (e.g. cyanopsia) (8,10,12), priapism (8–10), musculoskeletal pain (9) and haemodynamic (i.e. blood pressure and heart rate) changes (8–10) have been documented in patients taking PDE5is. These events may be related to a lack of exclusive selectivity for PDE5 with cross-reactivity occurring in the tissues of other PDE isozymes (e.g. PDE1: heart; PDE6: retina; and PDE11: skeletal muscle) (11).

Avanafil is a highly specific, rapidly acting PDE5i with a relatively short half-life that has recently been approved by the US Food and Drug Administration (FDA) for the treatment of ED (13). In phase 1 clinical trials, avanafil demonstrated single-dose pharmacokinetics with a mean time to maximum plasma concentration ($T_{\text{max}}$) ranging from 30 to 45 min and a terminal half-life of 3–5 h. Similarly, values for maximum concentration and area under the curve increase in a linear manner over a dose range of 12.5–200 mg, with no accumulation of drug observed in multiple-dose pharmacokinetic studies of 2 weeks’ duration (14).

Outcomes from phase 2 and phase 3 studies showed that, when administered in doses between 50 mg and 200 mg, avanafil has a favourable safety profile, with an improvement in sexual function in male patients with and without diabetes and following nerve-sparing radical prostatectomy (15–19). In two 12-week, phase 3 trials in male patients with (study TA-302) or without (study TA-301) diabetes, avanafil was shown to be well tolerated and effective in male patients with mild to severe ED, with no required restrictions of food or alcohol intake. Treatment response occurred as quickly as 15 min, and, in some patients, beyond 6 h after dosing (15,17). Based on the efficacy and safety outcomes of an integrated analysis of the phase 2 (TA-05) and phase 3 (TA-301 and TA-302) studies, an avanafil starting dose of 100 mg is recommended (15). Subgroup analyses of this integrated cohort, however, have indicated clinically relevant improvements in sexual function with the 200-mg dose in patients aged ≥ 65 years; with diabetes; with severe ED at baseline; and with ED ≥ 5 years’ duration. What is more, in these difficult to treat populations, improvement in sexual function was observed without any material increase in the nature or extent of AEs (20).

With short-term (12-week) efficacy and safety established, the objective of this study was to evaluate long-term (52-week) safety, tolerability and efficacy of avanafil in male patients with mild to severe ED, with or without diabetes, from the TA-301 and TA-302 populations.

**Methods**

**Study design**

This was a phase 3, 52-week, open-label extension trial for adult males with ED who had completed either of the phase 3, 12-week pivotal trials. Both 12-week trials were designed as randomised, double-blind, placebo-controlled studies of male patients with mild-to-severe ED, who were in monogamous, heterosexual relationships. One trial excluded patients with diabetes mellitus (TA-301); the other only enrolled patients with type 1 or 2 diabetes mellitus (TA-302). Patients were permitted to continue treatment with alpha-adrenergic antagonists (α-blockers) if on a stable dose for at least 14 days prior to study entry.

 Investigators received approval for the study protocol from their respective institutional review boards and obtained signed informed consent forms from trial participants.

**Patients**

Patients were required to have completed the entire treatment period in either of the previous phase 3 studies and to have demonstrated and documented compliance with the study protocol. They were required to make at least four attempts at sexual activity during each month of participation. They also had to agree not to take any other ED treatments of any kind. Patients were excluded if they had developed one or more comorbidities that posed a safety concern for continuation of treatment with avanafil during the trial or if they required treatment with a medication excluded by the protocol (e.g. nitrates, protease inhibitors, 5-α-reductase inhibitors).

**Dosing and administration**

All patients in this planned extension trial were initially assigned to treatment with avanafil 100 mg, but, upon request, they were permitted to increase their dose to 200 mg (for increased efficacy) or to decrease their dose to 50 mg (for improved tolerability). Participants were instructed to take one dose of
the study drug approximately 30 min prior to the initiation of sexual activity. Patients were permitted to take up to two doses of study drug per 24-h period provided that the doses were separated by at least 12 h. There were no restrictions placed on the consumption of food or alcohol.

Assessments and outcomes

Patients were instructed to maintain a diary of attempts at sexual activity and sexual experience that included Sexual Encounter Profile (SEP) and International Index of Erectile Function (IIEF) questions. SEP questions included ‘Were you able to insert your penis into your partner’s vagina?’ (SEP2) and ‘Did your erection last long enough for you to have successful intercourse?’ (SEP3). The IIEF is a validated, self-administered questionnaire that includes 15 questions (five domains) constructed to measure erectile function (21).

Efficacy variables for this study included a change in percentage of sexual attempts between the run-in period of the qualifying study and the treatment period of this study in which patients were able to maintain an erection of sufficient duration to have successful intercourse (SEP3); change in percentage of sexual attempts between the run-in period of the qualifying study and the treatment period of this study in which patients were able to insert the penis into the partner’s vagina (SEP2); and the change in mean IIEF erectile function (IIEF-EF) domain score from baseline to end of treatment.

Other efficacy variables included the proportion of patients with an IIEF-EF domain score in the normal range (≥ 26) at the end of treatment and the proportion of successful responses to diary questions by time interval.

Subgroup analyses of each primary efficacy variable (SEP2, SEP3 and IIEF-EF) were performed for patients on the basis of age (< 50 years, 50–64 years and ≥ 65 years), race (white, black, Asian and multiple races), baseline ED severity (mild, moderate and severe) and duration of ED (< 24 months, 24–59 months and ≥ 60 months). Post hoc analyses were also performed for the subgroups of patients with or without diabetes at baseline.

Safety outcomes of interest included the evaluation of AEs, clinical laboratory values, vital signs, physical examinations and electrocardiogram readings.

Statistical analysis

The primary analysis population for efficacy outcomes was the intent to treat (ITT) population, defined as all patients who took ≥ 1 dose of study drug and had ≥ 1 postdose efficacy assessment. The safety population consisted of all rollover patients from the 12-week trials who signed the informed consent; this population was used for all safety analyses.

Summary statistics for all efficacy outcomes were analysed by avanafil dosage: patients receiving 100 mg only throughout the trial; patients receiving both 100 mg and 200 mg; other dosage combinations; and overall population.

Results

Baseline demographics and avanafil exposure

A total of 712 patients were enrolled in this 52-week extension trial. Enrollment was closed early after meeting the FDA’s enrollment and drug-exposure requirements (≥ 300 patients with ≥ 6 months of total exposure and ≥ 100 patients with ≥ 12 months of total exposure).

Baseline demographics and characteristics were similar in each treatment group (Table 1). The total study population was predominantly white, with a mean age of 56.4 years. ED was rated as mild, moderate and severe in 29.1%, 33.4% and 37.5% of patients, respectively. The mean duration of ED in this population was > 5 years, and approximately 32% of patients were previously diagnosed with diabetes mellitus. Certain concomitant medications were allowed in this trial; 46% of patients in the safety population were being treated with antihypertensives, 8% were taking antidepressants and 6% were taking β-blockers.

In all, 171 patients (24.0%) received avanafil 100 mg only. A high proportion (n = 536; 75.3%) of patients requested that their avanafil dose be increased to 200 mg; this group therefore received both avanafil 100 mg and 200 mg during the study. Only three patients (0.4%) requested that their avanafil dose be decreased and so received avanafil 100 mg and 50 mg, one patient (0.1%) received all three doses and one patient (0.1%) did not receive any study drug. In all, 492 patients (69.1%) completed this trial (Figure 1).

Efficacy outcomes

Patients showed clinical improvements for all primary efficacy outcomes (Figure 2). Treatment with avanafil was associated with improvements in SEP2, from 44.1% at baseline of the qualifying study to 83.3% during the treatment period (100-mg group) and from 43.0% at baseline to 79.4% during treatment (100 mg/200-mg group). Improvements in SEP3 were approximately five times greater during treatment compared with baseline in both dosage groups; more than 65% of patients in both dosage groups reported achieving successful intercourse. The mean IIEF-EF domain score improved from 13.6 at
baseline to 22.2 in the 100-mg group and from 11.9 at baseline to 22.7 in the 100/200-mg group.

Overall, normalisation of IIEF-EF domain score (≥ 26) at the end of treatment was reported in 64.0%, 55.1% and 36.0% of patients with mild, moderate and severe ED, respectively.

Successful intercourse (SEP3) was demonstrated by some patients within 15 min of dosing and greater than 6 h postdosing with avanafil (Figure 3).

In patients attempting sexual intercourse within 15 min of dosing, 83% (169/203) were successful. In patients attempting sexual intercourse greater than 6 h after dosing, 74% (48/65) were successful. A total of 84% of all sexual attempts were made within 60 min of dosing.

Within the ITT population, 512 patients who initiated treatment with the 100-mg dose requested a dose increase to 200 mg. Of these, 172 patients (33.6%) were nonresponders to the 100-mg dose (with response defined by a positive change from baseline in SEP3 during the first 30 days of the trial). Among the 172 patients who were nonresponders to the 100-mg dose, 112 (65.1%) went on to respond to the 200-mg dose. A higher study-retention rate was reported among patients who escalated to the 200-mg dose compared with those who only received the 100-mg dose (74% vs. 54%).

**Subgroup analyses**

The effects of avanafil treatment on erectile function were observed across subgroups by age, baseline ED severity, duration of ED, baseline diabetic status and race.

**Age**

Overall (regardless of avanafil dose), for patients aged < 50 years, 50–64 years and ≥ 65 years, respectively, the mean change from baseline to the treatment period for SEP2 was 26.2%, 37.3% and 45.0%; the mean change in SEP3 was 59.6%, 62.7% and 44.0% and the mean change in IIEF-EF domain score was 8.5, 10.7 and 11.4, respectively (Figure 4). For patients aged ≥ 65 years, the mean change from baseline to end of treatment in SEP3 and IIEF-EF was significantly greater in the avanafil 100 mg/200-mg group (42.4%) than in the avanafil 100-mg group (24.6%) (p < 0.05).

**Baseline severity of ED**

Overall (regardless of avanafil dose), for patients with mild, moderate and severe ED at baseline, the mean change from baseline to the treatment period for SEP2 was 26.2%, 37.3% and 45.0%; the mean change in SEP3 was 59.6%, 62.7% and 44.0% and the mean change in IIEF-EF domain score was 8.5, 10.7 and 11.4, respectively (Figure 5). For patients with moderate or severe ED, the mean change from baseline to end of treatment in SEP3 and IIEF-EF was greater in the avanafil 100 mg/200-mg group than in the avanafil 100-mg group.

**Baseline duration of ED**

Overall (regardless of avanafil dose), for patients with duration of ED of < 24 months, 24–59 months and ≥ 60 months at baseline, the mean change from

---

**Table 1 TA-314: baseline demographics and characteristics (enrolled patients)**

| Patient characteristic | Avanafil 100 mg only (n = 171) | Avanafil 100 and 200 mg*, † (n = 536) | Total‡, †, ‡ (N = 712) |
|------------------------|-------------------------------|----------------------------------|------------------------|
| Mean age, years (SD)   | 54.2 (10.9)                   | 57.1 (9.9)                       | 56.4 (10.2)            |
| White, n (%)           | 147 (86.0)                    | 459 (85.6)                      | 610 (85.7)             |
| ED severity, n (%)     |                               |                                 |                        |
| Mild                   | 64 (37.4)                     | 142 (26.5)                      | 207 (29.1)             |
| Moderate               | 59 (34.5)                     | 177 (33.0)                      | 236 (33.4)             |
| Severe                 | 48 (28.1)                     | 217 (40.5)                      | 267 (37.5)             |
| Mean ED duration, months (SD) | 63.7 (58.6) | 79.8 (72.3) | 75.9 (69.4) |
| History of diabetes, n (%) |                          |                                 |                        |
| Type 1                 | 6 (3.5)                       | 14 (2.6)                        | 20 (2.8)               |
| Type 2                 | 57 (33.3)                     | 148 (27.6)                      | 206 (28.9)             |

* Patients who received both avanafil 100 mg and 200 mg over the course of the study. Some patients switched immediately (visit 2), whereas others waited until visit 3.
† During the course of the study, patients were permitted to increase their avanafil dose to 200 mg (for increased efficacy) or decrease their dose to 50 mg (for improved tolerability). ‡ Three patients received avanafil 100 mg and 50 mg, one patient received all three doses of avanafil and one patient did not receive study drug during this extension study.
ED, erectile dysfunction; SD, standard deviation.
baseline to the treatment period for SEP2 was 40.7%, 39.9% and 33.7%; the mean change in SEP3 was 61.1%, 64.9% and 45.8%; and the mean change in IIEF-EF domain score was 10.9, 11.9 and 9.1, respectively (Figure 6). There were no differences noted between avanafil dosage groups.
Diabetic vs. nondiabetic status
Among all patients who took avanafil 100 mg and 200 mg and among both subgroups of patients with diabetes and patients without diabetes, the percentage of sexual attempts resulting in successful vaginal penetration (SEP2) and successful intercourse (SEP3) was higher with avanafil 200 mg than with avanafil 100 mg (Figure 7).

Figure 5 Coprimary end points (SEP2, SEP3, and IIEF-EF) at baseline and end of treatment by severity of erectile dysfunction (ITT population), %. IIEF-EF, International Index of Erectile Function–Erectile Function domain score; ITT, intent to treat; SEP2, Sexual Encounter Profile question 2 (successful vaginal insertion); SEP3, Sexual Encounter Profile question 3 (successful intercourse)

Figure 6 Coprimary end points (SEP2, SEP3, IIEF-EF) at baseline and end of treatment by baseline duration of erectile dysfunction (ITT population), %. IIEF-EF, International Index of Erectile Function–Erectile Function domain score; ITT, intent to treat; SEP2, Sexual Encounter Profile question 2 (successful vaginal insertion); SEP3, Sexual Encounter Profile question 3 (successful intercourse)

Diabetic vs. nondiabetic status
Among all patients who took avanafil 100 mg and 200 mg and among both subgroups of patients with diabetes and patients without diabetes, the percentage of sexual attempts resulting in successful vaginal penetration (SEP2) and successful intercourse (SEP3) was higher with avanafil 200 mg than with avanafil 100 mg (Figure 7).

Figure 7 Coprimary end points (SEP2 and SEP3) during treatment period, by diabetes status: patients who took both avanafil 100 mg and 200 mg (ITT population), mean (SD), %. *Per cent difference between avanafil 100 mg and 200 mg. ITT, intent to treat; SD, standard deviation; SEP2, Sexual Encounter Profile question 2 (successful vaginal insertion); SEP3, Sexual Encounter Profile question 3 (successful intercourse)
Race subgroup

Overall, there were no significant differences between black patients and white patients, respectively, in the per cent mean change from baseline to the treatment period for SEP2 (32.2% and 37.6%) and SEP3 (58.9% and 54.1%) success rates, or in IIEF-EF domain scores (10.9 and 10.2). There were also no significant differences between black and white patients regarding response to avanafil dose. The subgroups of Asian patients (n = 6) and patients of multiple races (n = 1) were of insufficient sample size to make meaningful comparisons with the subgroups of white and black patients.

Safety outcomes

The most frequently reported treatment-emergent AEs (TEAEs) were similar to those reported with other PDE5is: headache, flushing, nasopharyngitis and nasal congestion (Table 2). A total of 275 (38.7%) patients experienced a TEAE; in 79 (11.1%) patients, these events were considered drug-related. Eleven (1.5%) patients experienced a serious AE, none of which were considered drug-related. No deaths were reported during this trial.

The overall discontinuation rate was 30.9%; discontinuations due to AEs occurred in 20 (2.8%) patients (see Figure 1). The percentage of patients who discontinued from the study was lower among those who received avanafil 100 mg/200 mg (25.9%) than among those who received only avanafil 100 mg (46.2%). Discontinuations caused by AEs were also lower among those who received avanafil 100 mg/200 mg (1.5%) than among those who received avanafil 100 mg only (6.4%).

Two events of cyanopsia were reported in one patient (0.1%); there were no reports of hearing loss. Two events of increased erection were reported (0.4%) along with one report of spontaneous erection, but none of these met the clinical definition of priapism. There were no TEAEs classified as major cardiac events. Ten (1.4%) patients experienced haemodynamic changes: nine (1.3%) patients with dizziness and one (0.1%) with vasovagal syncope.

Mean exposure to avanafil in this population was 35.3 weeks, with 153 (21.5%) patients being exposed to study drug ≥ 52 weeks.

Discussion

The data presented here suggest that avanafil is an effective, long-term treatment for ED, with improvements observed at up to 1 year. Avanafil demon-

### Table 2 Summary of adverse events (safety population)

| Patients with an AE, n (%) | Avanafil 50 mg (n = 4) | Avanafil 100 mg (n = 711) | Avanafil 200 mg (n = 514) | Total (N = 711) |
|----------------------------|------------------------|--------------------------|--------------------------|----------------|
| **Patients with any TEAEs** |                        |                          |                          |                |
| Any TEAEs                  | 3 (75.0)               | 135 (19.0)               | 183 (35.6)               | 275 (38.7)     |
| Any drug-related TEAE      | 3 (75.0)               | 42 (5.9)                 | 50 (9.7)                 | 79 (11.1)      |
| **Patient with SAEs**      |                        |                          |                          |                |
| Any SAE                    | 0 (0.0)                | 6 (0.8)                  | 5 (1.0)                  | 11 (1.5)       |
| Any TESAE                  | 0 (0.0)                | 6 (0.8)                  | 5 (1.0)                  | 11 (1.5)       |
| Any drug-related SAE       | 0 (0.0)                | 0 (0.0)                  | 0 (0.0)                  | 0 (0.0)        |
| **Discontinuations due to AEs** |                     |                          |                          |                |
| Any AE                     | 1 (25.0)               | 13 (1.8)                 | 6 (1.2)                  | 20 (2.8)       |
| Any TEAE                   | 1 (25.0)               | 13 (1.8)                 | 6 (1.2)                  | 20 (2.8)       |
| Any drug-related TEAE      | 1 (25.0)               | 6 (0.8)                  | 3 (0.6)                  | 10 (1.4)       |
| Any SAE                    | 0 (0.0)                | 5 (0.7)                  | 1 (0.2)                  | 6 (0.8)        |
| Deaths                     | 0 (0.0)                | 0 (0.0)                  | 0 (0.0)                  | 0 (0.0)        |
| **Most common (≥ 2%) TEAEs** |                      |                          |                          |                |
| Headache                   | 1 (25.0)               | 19 (2.7)                 | 27 (5.3)                 | 40 (5.6)       |
| Flushing                   | 0 (0.0)                | 10 (1.4)                 | 17 (3.3)                 | 27 (3.5)       |
| Nasopharyngitis            | 0 (0.0)                | 5 (0.7)                  | 20 (3.9)                 | 24 (3.4)       |
| Nasal congestion           | 0 (0.0)                | 8 (1.1)                  | 10 (1.9)                 | 18 (2.5)       |
| Influenza                  | 0 (0.0)                | 3 (0.4)                  | 8 (1.6)                  | 11 (1.5)       |
| Back pain                  | 0 (0.0)                | 4 (0.6)                  | 8 (1.6)                  | 11 (1.5)       |
| Upper respiratory infection| 0 (0.0)                | 5 (0.7)                  | 1 (0.2)                  | 6 (0.8)        |
| Dizziness                  | 1 (25.0)               | 6 (0.8)                  | 3 (0.6)                  | 9 (1.3)        |

AE, adverse event; SAE, serious AE; TEAE, treatment-emergent AE; TESAE, treatment-emergent SAE.
stratified a rapid onset of action, with success as early as 15 min, and, in some patients, the duration of effect was sustained beyond 6 h after dosing. The rapid and sustained efficacy is consistent with the pharmacokinetic profile of avanafil, which shows that avanafil is rapidly absorbed (median T\text{max} 30–45 min) following oral administration (14).

Clinical improvement was demonstrated for all primary efficacy outcomes, including rates of successful penetration (SEP2) and intercourse (SEP3), as well as improvement in erectile function per the IIEF. Normalisation of erectile function was reported by up to 64% of patients, depending upon the severity of ED at baseline.

For all avanafil doses, increases in the rate of successful sexual attempts (SEP2) and intercourse (SEP3) and improvement in IIEF-EF were observed among all subpopulations, including patients who were stratified by baseline severity, duration of ED, age, diabetes status and race. Dose-related improvements (SEP2, SEP3 and IIEF-EF) were reported across all subgroups with the exception of all ED severity subgroups (SEP2 and SEP3); ED duration < 24 months (SEP2, SEP3 and IIEF-EF) and black race (SEP2).

During the study, 75% of patients overall requested an increase in avanafil dose from 100 mg to 200 mg and experienced additional mean improvement in erectile function as measured by the primary end points. Approximately 66% of patients responded to the avanafil 100-mg dose, and, of those who did not, approximately 65% went on to respond to avanafil 200 mg, for an overall response rate of 75%. Among patients who escalated to the 200-mg dose, study-retention rates were higher compared with those patients who only received the 100-mg dose (74% vs. 54%). In the double-blind cohort (TA-301 and TA-302), 53% (n/N = 549/1032) of patients, overall, took two doses of study drug within 24 h. For these patients, the mean number of times during the study that two doses were taken within 24 h was 3.4.

Both avanafil 100 mg and 200 mg were generally well tolerated [mean duration of exposure, ~9 months (35.3 weeks)] and demonstrated an acceptable safety profile during this trial, which may be reflective of the low selectivity of avanafil towards other PDE isozymes (particularly PDE1, PDE6 and PDE11) (22). The rates of AEs that are of particular concern within the PDE5 class (i.e. hemodynamic changes, visual disturbance, priapism and cardiovascular events) were low. There were no reports of hearing loss or priapism, and only one patient reported cyanopsia. Discontinuations due to AEs were < 3%.

The open-label trial design can be considered a limitation of this study. All patients who completed either of the 12-week trials were invited to participate in this extension regardless of their response to treatment during the qualifying trials; however, it is possible that responders were more likely to enroll in the extension than nonresponders. Another potential limitation is the overall discontinuation rate of approximately 30%; however, < 3% of discontinuations were due to AEs. In addition, discontinuations were lower in patients who escalated to the highest dose compared with those who remained on the 100-mg dose.

**Conclusions**

This 52-week, open-label extension trial demonstrates that avanafil 100 mg or 200 mg is effective in improving erectile function in adult males with ED, with clinical improvement observed for up to 52 weeks and across all subgroups analysed, including by baseline severity of ED, baseline duration of ED, age, diabetes status and race. Data also suggest that for some individuals who do not achieve a satisfactory response to avanafil 100 mg, the administration of avanafil 200 mg may result in an improvement in response (in both diabetic and nondiabetic populations).

Avanafil was shown to be generally well tolerated over 52 weeks. The long-term tolerability and improvement in sexual function, coupled with the rapid onset of action, suggest that avanafil is well suited for the on-demand treatment of mild to severe ED.

**Author contributions**

All authors contributed to the critical analysis of the content of this manuscript, as well as providing contributions to the discussion. All authors reviewed and edited this manuscript. Dr. Belkoff takes responsibility as the guarantor for the contents of this manuscript and was involved in writing, reviewing and editing this manuscript. Drs. McCullough, Goldstein and Jones also contributed to the writing of this manuscript. Dr. Bowden, Ms. DiDonato, Ms. Trask and Dr. Day were involved in protocol writing, the statistical analysis plan development, and development of the final clinical study report.

**Acknowledgements**

We acknowledge and thank the TA-314 investigators and study coordinators, the Quintiles team (study CRO), The Lockwood Group and KnowledgePoint360 Group, LLC (for editorial assistance, funded by VIVUS, Inc) and VIVUS internal contributors. VIVUS designed and funded this study, VIVUS also wrote the study protocol and funded the data analysis.
References
1 Selvin E, Burnett AL, Platz EA. Prevalence and risk factors for erectile dysfunction in the US. Am J Med 2007; 120: 151–7.
2 Feldman H, Goldstein I, Hatzichristou DG et al. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994; 151: 54–61.
3 Johannes CB, Araujo AB, Feldman HA et al. Incidence of erectile dysfunction in men 40-69 years old: longitudinal results from the Massachusetts male aging study. J Urol 2000; 163: 460–3.
4 Corbin JD. Mechanisms of action of PDE5 inhibition in erectile dysfunction. Int J Impot Res 2004; 16(Suppl 1): S4–7.
5 Corona G, Mondaini N, Ungar A et al. Phosphodiesterase type 5 (PDE5) inhibitors in erectile dysfunction: the proper drug for the proper patient. J Sex Med 2011; 8: 3418–32.
6 Schouten BW, Bohnen AM, Groeneveld FP et al. Erectile dysfunction in the community: trends over time in incidence, prevalence, GP consultation and medication use – the Krimpen study: trends in ED. J Sex Med 2010; 7: 2547–53.
7 Eardley I, Donatucci C, Corbin J et al. Pharmacotherapy for erectile dysfunction. J Sex Med 2010; 7(1 Pt 2): 524–40.
8 Pfizer Labs. Viagra (package insert). New York, NY: Pfizer Labs, 2010.
9 Eli Lilly and Company, Cialis (package insert). Indianapolis, IN: Eli Lilly and Company, 2011.
10 Bayer HealthCare Pharmaceuticals, Inc. Levitra (package insert). Wayne, NJ: Bayer HealthCare Pharmaceuticals Inc., 2011.
11 Bischoff E. Potency, selectivity, and consequences of nonselectivity of PDE inhibition. Int J Impot Res 2004; 16: S11–4.
12 Giuliano F, Jackson G, Montorsi F et al. Safety of sildenafil citrate: review of 67 double-blind placebo-controlled trials and the postmarketing safety database. Int J Clin Pract 2010; 64: 240–55.
13 VIVUS, Inc. STENDRA (package insert). Mountain View, CA: VIVUS, Inc., 2012.
14 Allison M, Grant T, Obaidi M et al. Pharmacokinetics of avanafil, a novel, rapidly absorbed, selective PDE5 inhibitor for the treatment of mild to severe erectile dysfunction. J Sex Med 2011; 8: S466–7.
15 Goldstein I, McCullough AR, Jones LA et al. Avanafil for the treatment of erectile dysfunction: a multicenter, randomized, double-blind study in men with diabetes. Mayo Clin Proc 2012; 87: 843–52.
16 Kaufman J, Dietrich J. Safety and efficacy of avanafil, a new PDE5 inhibitor for treating erectile dysfunction. J Sex Med 2006; 3: 14–69.
17 Mulhall JP, Moul JW, Wang R et al. A phase III, placebo-controlled study of the safety and efficacy of avanafil in the treatment of erectile dysfunction following bilateral, nerve-sparing radical prostatectomy. J Sex Med 2012; 9: 542–3.
18 Mulhall JP, Burnett AL, McVary KT et al. Efficacy and safety of avanafil, a next-generation, phosphodiesterase type 5 inhibitor for the treatment of men with erectile dysfunction: data from phase 2 and 3 studies in difficult-to-treat populations. Oral presentation at: the American Urological Association (AUA) Annual Meeting; 19–23 May 2012; Atlanta, GA, USA.
19 Rosen RC, Riley A, Wagner G et al. The International Index of Erectile Function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology 1997; 49: 822–30.
20 Kotera J, Mochida H, Inoue H et al. Avanafil, a potent and highly selective phosphodiesterase-5 inhibitor for erectile dysfunction. J Urol 2012; 188: 668–74.

Paper received June 2012, accepted September 2012