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Sponsor: Sanofi **Drug substance(s):** Avanafil	**Study Identifiers:** U1111-1167-6889, NCT02503306 **Study code:** AVANAL07163

Title of the study: Clinical study of efficacy and tolerability of single doses of avanafil 100 mg and 200 mg in patients with erectile dysfunction in Russian Federation

Study center(s): 7 study centers in Russia

Study period:

Date first patient enrolled: 24/Jul/2015

Date last patient completed: 14/Mar/2016

Phase of development: Phase 3

Objectives:

Primary objectives

- Change from baseline (run-in period before treatment) in the percentage of sexual attempts when patients were able to maintain the erection long enough to successfully terminate the sexual act, after 8 weeks of treatment (SEP3, Subject's diary, question 5).
- Change from baseline (run-in period before treatment) in the percentage of sexual attempts when patients were able to maintain the erection to successfully penetrate the partner's vagina, after 8 weeks of treatment (SEP2, Subject's diary, question 4).
- Changes in erectile dysfunction index (International Index of Erectile Function (IIEF) questionnaire) from baseline (at the moment of inclusion, Visit 2) at the end of the treatment.

Additional objective

To evaluate safety and tolerability of single doses of avanafil 100 mg and 200 mg in tablets in patients with erectile dysfunction.

Methodology: Prospective, multicenter, randomized, double blind, placebo-controlled, parallel groups clinical study.

Number of patients**:** Planned: 189 patients, 63 in each therapy group

Randomized: 189

Treated: 179 (PP-population)

Evaluated:

Efficacy: 179

Safety: 189

Diagnosis and criteria for inclusion: Male patients from ≥ 18 to ≤ 70 years old with mild, moderate, or severe erectile dysfunction during at least the last 6 months and monogamous heterosexual relationship during at least 3 months before the start of the study participation, who agree to make at least 4 sexual attempts per month

Study treatments

Investigational medicinal product(s): Placebo 100 mg and 200 mg; Avanafil 100 mg and 200 mg

Formulation: Film-coated tablets

Route of administration: Oral

Dose regimen: Avanafil 100 mg + Placebo 100 mg; Avanafil 100 mg + Avanafil 100 mg; Placebo 100 mg + Placebo 100 mg

Duration of treatment: 8 weeks

Duration of observation: Clinical study duration for each patient will be 12 weeks (about 3 months)

Criteria for evaluation:

Efficacy:
Primary endpoints

- Change from baseline (run-in period before treatment) in the percentage of sexual attempts when patients were able to maintain the erection long enough to successfully terminate the sexual act, after 8 weeks of treatment (SEP3, Subject's diary, question 5).
- Change from baseline (run-in period before treatment) in the percentage of sexual attempts when patients were able to maintain the erection to successfully penetrate the partner's vagina, after 8 weeks of treatment (SEP2, Subject's diary, question 4).
- Changes in erectile dysfunction index (IIEF questionnaire) from baseline (at the moment of inclusion, Visit 2) at the end of the treatment.

Safety:

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Differences in safety and tolerability of single doses of Avanafil 100 mg and 200 mg in tablets in patients with erectile dysfunction, according to the International Erectile Dysfunction Index questionnaire.

Statistical methods: Statistical power and sample size: taking into account the interventional nature of the study and the fact that the analysis will be performed in several subgroups, the sample size of 189 patients will provide the power of 80% at the alfa of 0.017 to avoid multiplicity of comparisons.

Summary:

Population characteristics:

All in all 189 male patients aged 47.22±13.21 years (mean±SD) were enrolled in the study (ITT population). 10 patients were excluded from the efficacy analysis: 8 patients were excluded due to their non-compliance to the visit schedule, 1 patient was lost to follow-up and 1 patient was excluded due to protocol deviation. Efficacy analysis was performed in the PP population which comprised of 179 patients who met all the inclusion and none of the exclusion criteria. Patients in the PP population were stratified into three sub-groups according to the severity of the erectile dysfunction using the baseline IIEF EF score: patients with mild (n=59; 32.96%), moderate (n=57; 31.84%), or severe (n=63; 35.19%) erectile dysfunction. At baseline, the percentages of sexual attempts when patients were able to maintain the erection long enough to successfully terminate the sexual act, were equal across the three treatment groups (21.43%; 27.71%; 24.09% in placebo, avanafil 200 mg, and avanafil 100 mg dosing groups, respectively, Z-test p>0.05). The most common conditions registered in the medical history of patients included in the ITT population were as follows: infections and infestations (n=13; 6.88%) across all treatment groups; injuries (n=6; 3.17%) including foot fracture (n=2; 3.17%) in placebo group, spinal injury (n=1; 1.59%) in avanafil 100 mg dosing group, and testicular injury (n=1; 1.59%) in avanafil 200 mg dosing group; reproductive system disorders except erectile dysfunction (n=5; 2.65%) included varicocele (n=1; 1.59% and n=2; 3.17%) in avanafil 200 mg, and avanafil 100 mg dosing groups, respectively.

Efficacy results:

- Change from baseline in the percentage of sexual attempts when patients were able to maintain the erection long enough to successfully terminate the sexual act, after 8 weeks of treatment (SEP3, Subject's diary, question 5) comprised 28.13% in the placebo group, and 49.44% and 41.58% in 200 mg and 100 mg avanafil dosing groups, respectively. According to the analysis of the 95% CI, the difference in this parameter between the placebo and each of the avanafil dosing groups was statistically significant and dose-dependent. The percentages of sexual attempts when patients were able to maintain the erection long enough to successfully terminate the sexual act, were 21.43%; 27.71%; 24.09% in placebo, avanafil 200 mg, and avanafil 100 mg dosing groups, respectively, at baseline and 49.56%; 77.15%; 65.67% in placebo, avanafil 200 mg, and avanafil 100 mg dosing groups, respectively, after treatment.
- The maximum changes from baseline in the percentage of sexual attempts when patients were able to maintain the erection long enough to successfully terminate the sexual act after 8 weeks of treatment (SEP3, Subject's diary, question 5) were observed in 200 mg and 100 mg avanafil dosing groups in patients with moderate and severe ED degrees: 51.94% in 200 mg avanafil group and 34.06% in 100 mg avanafil group for moderate ED degree and 46.09% in 200 mg avanafil group and 26.50% % in 100 mg avanafil group for severe degree.
- There was no statistically significant difference between treatment groups in change from baseline (run-in period before treatment) in the percentage of sexual attempts when patients were able to maintain the erection to successfully penetrate the partner's vagina, after 8 weeks of treatment (SEP2, Subject's diary, question 4): 16.86 % in the placebo group, and 21.16% and 25.44% in 200 mg and 100 mg avanafil dosing groups, respectively, as the 95% confidence intervals were overlapping by a big margin. The percentages of sexual attempts when patients were able to maintain the erection to successfully penetrate the partner's vagina, were 58.04%; 67.83%; 60.37% in placebo, avanafil 200 mg, and avanafil 100 mg dosing groups, respectively, at baseline and 74.89%; 89%; 85.91% in placebo, avanafil 200 mg, and avanafil 100 mg dosing groups, respectively, after treatment.
- According to two-way repeated measures ANOVA, the variables Time, Group, and their combination have demonstrated the statistically significant impact on the changes in erectile dysfunction index (IIEF) questionnaire). The Tukey HSD post-hoc test has shown the statistically significant difference in the IIEF score change from baseline between placebo and avanafil 200 mg dosing groups: in avanafil 200 mg group the mean score comprised 14.02±4.98 at baseline and 22.17±6.06 at Visit 4 whereas in placebo group the mean score was 13.77±5 at baseline and only 17.65±6.75 at Visit 4. The other pairwise comparisons between the treatment groups failed to demonstrate the statistically significant difference for this parameter.

Safety results:

- 189 subjects analyzed (ITT population)
- Four patients (2.12%) reported four AEs in the pre-treatment period: two (3.17%) in the placebo group and one (1.59%) in both of the groups on avanafil 200 mg and 100 mg. These included mild rhinitis (n=1) in the placebo group (the AE resolved spontaneously and did not require to discontinue or quit the treatment), mild non-specific acute sinusitis (n=1) in avanafil 200 mg and mild erysipelas (n=1) in avanafil 100 mg dosing groups; in both cases, the specific therapy resulted in full recovery of the events. In addition, one patient in placebo group developed mild renal colic, for which the patient was given the therapy with full recovery.
- Eight subjects (12.70%) reported 9 treatment-emergent adverse events (TEAEs), 7 of mild and 2 of moderate severity, in the avanafil 200 mg group and 12 subjects (19.05%) reported 16 mild treatment-emergent adverse events (TEAEs) in the avanafil 100 mg group, with no patients who had TEAEs in the placebo group. Of 16 TEAEs in avanafil 100 mg group 5 TEAEs were considered IP related and 11 IP non-related whereas of 9 TEAEs in avanafil 200 mg group 6 TEAEs were considered IP related and 3 IP non-related.
- The most common TEAEs were related to infections (herpes zoster, acute bronchitis, respiratory tract viral infection; n=3; 1.59%) and nervous system disorders (headache and intermittent headache). Headache (n=8; 4.23%) was only reported by patients receiving avanafil 200 mg (n=3; 4.76%) or avanafil 100 mg (n=5; 7.94%). Moreover, one episode of moderate intermittent headache (n=1; 1.59%) was reported in the avanafil 200 mg dosing group: the AE recovered spontaneously and did not require discontinuation or quitting the IP. Both headache and intermittent headache were seen as IP-related whereas infections were regarded as IP-unrelated TEAEs.
- Of all TEAEs, 1 TEAE (herpes zoster infection, moderate severity) was serious, for which the patient was hospitalized with the specific therapy prescribed, which resulted in full recovery of the event and the treatment with IP was not discontinued or quit. This SAE was not considered IP related.
- There were clinically significant abnormalities in physical assessment data observed at visits 1 (1 patient with obesity) and 3 (1 patient with arise in blood pressure level), whereas the clinically significant abnormalities were not found at visits 2 and 4. The pairwise comparison (via Fisher's test) failed to recognize statistical significance in the number of clinically significant abnormalities in physical assessment between the treatment groups across the visits.
- Mann-Whitney test demonstrated no statistically significant differences for demographics and vital signs variables between treatment groups across visits, excepting body temperature (placebo vs. avanafil 200 mg and placebo vs. avanafil 100 mg), which, however, was not clinically significant.

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