

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
200179Orig1s000

STATISTICAL REVIEW(S)

STATISTICS FILING MEMORANDUM FOR A NEW NDA

NDA: 200-179
Drug Name: Vardenafil Hydrochloride (10 mg tablet, orally disintegrating)
Sponsor: Bayer HealthCare Pharmaceuticals Inc.
Indications: Treatment of erectile dysfunction
Medical Officer: Donald McNellis, M.D., Division of Reproductive and Urology Products
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Project Manager: Eufrecina P Deguia
Submission Date: 08/26/2009
45 day Meeting Date: 10/14/2009

A: Summary of Clinical Studies

The objective of this filing review is to determine whether this NDA is sufficiently complete for substantive statistical review. As part of the determination, we verify the format and contents of the safety and efficacy data sets that will allow us to perform pertinent statistical analysis as per study protocol. The sponsor submitted two pivotal Phase-III placebo-controlled studies to support the efficacy of Vardenafil Hydrochloride in the treatment of erectile dysfunction. These studies are entitled as follows.

1. Study 12094 (A45684): Pivotal phase III trial to investigate the efficacy and safety of an Orodispersible Tablet vardenafil versus placebo in the treatment of men with Erectile dysfunction (ED) – a fixed-dose, double-blind, randomized multi-center Trial – POTENT II
2. Study 12093 (A44851): Pivotal phase III trial to investigate the efficacy and safety of an Orodispersible Tablet vardenafil versus placebo in the treatment of men with Erectile dysfunction (ED) – a fixed-dose, double-blind, randomized multi-center Trial – POTENT I

Both studies have the same three co-primary efficacy endpoints: (1) IIEF-EF Domain score at Visit 4 (Week 12) using last observation carry forward (LOCF), (2) SEP 2 (success rates of penetration) at Visit 4 (Week 12), and (3) SEP 3 (maintenance of erection) at Visit 4 (Week 12). The treatment period is 12 weeks.

The sponsor's results show (Table A.1) that all three co-primary endpoints are statistically significantly improved when compared to placebo. These results will be verified during the review of this application.

Table A.1 Summary of Sponsor's Efficacy Results Based on the Three Co-primary Endpoints						
Study	Endpoint	Vardenafil		Placebo		P-value
		N	Least Squares Mean	N	Least Squares Mean	
12093 (A44851)	IIEF-EF	181	21.48	172	14.38	<0.0001
	SEP 2	179	73.73	169	46.68	<0.0001
	SEP 3	178	64.89	164	26.70	<0.0001
12094 (A45684)	IIEF-EF	167	20.80	160	13.88	<0.0001
	SEP 2	168	68.99	161	43.02	<0.0001
	SEP 3	168	60.02	160	26.59	<0.0001

Source: Tables 11-6, 11-8, 11-10 in both studies

STATISTICS FILING MEMORANDUM FOR A NEW NDA

B: Conclusion

After preliminary review of the submission for the following items in the checklist, we have determined that this NDA is fileable.

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)		√		Annotated CRF is missing.
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			NA for Gender
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).		√		Analysis and tabulation datasets are combined in one folder

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			√	
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	√			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

Information requests for the Applicant:

1. Provide the location of the annotated CRFs or submit them to the application.
2. Provide the details of how you score each answer in IIEF-EF. The provided “bay38-9456-questionnaire-scoring-calculations-v8-1-final.pdf” is not sufficient. You only provided the scores you used, but did not provide the corresponding answers except for IIEF01.
3. The analysis and tabulation datasets are in one folder of the submission. They should be in separate folders, one for the analysis datasets and one for the tabulation datasets.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIN FANG
10/15/2009

SONIA CASTILLO
10/15/2009
Signing for Mahboob Sobhan



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 200-179/N0000

Drug Name: Staxyn (Vardenafil Hydrochloride Orodispersible Tablets, 10 mg)

Indication(s): Treatment of erectile dysfunction

Applicant: Bayer HealthCare Pharmaceuticals Inc.

Date(s): Date of submission: August/26/2009
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Review Priority: Standard

Biometrics Division: Division of Biometrics 3

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Data from two Phase 3 studies support the efficacy of Staxyn (vardenafil orodispersible tablet 10 mg) in the treatment of erectile dysfunction as demonstrated by statistically significant increases in erectile function score, rate of successful penetration, and Maintenance of erection after 12 weeks of treatment.

From statistical perspective, this application provided adequate data to support the efficacy of Staxyn in the treatment of ED patients.

1.2 Brief Overview of Clinical Studies

The sponsor, Bayer HealthCare Pharmaceuticals Inc, submitted efficacy and safety data from two Phase 3 studies (Studies 12093 and 12094) to support Staxyn in the treatment of patients with erectile dysfunction (ED). Study 12093 was conducted in Europe and South Africa across 40 centers in Belgium, France, Germany, Spain, South Africa, and Netherlands. Study 12094 was conducted across 35 centers in Australia, Canada, Mexico, and in the US. Men of age ≥ 18 with a history of ED for at least 6 months who also satisfied other inclusion/exclusion criteria were randomized to receive either Staxyn or matching placebo during 12 weeks of treatment period after 4 weeks of no-treatment run-in period. The randomization was stratified by age (<65 or ≥ 65).

The primary objective of both the studies was to compare the efficacy and safety of the Staxyn with the matching placebo in men with ED. The three co-primary endpoints included: (1) International Index of Erectile Function, Erectile Function (IIEF-EF) Score, (2) Sexual Encounter Profile Question 2 (SEP-2), and (3) Sexual Encounter Profile Question 3 (SEP-3). The treatment duration was 12 weeks.

At the end of Study 12093, 362 subjects were randomized, out of which 355 subjects were analyzed for efficacy. At the end of Study 12094, 339 subjects were randomized, out of which 331 subjects were analyzed for efficacy

1.3 Statistical Issues and Findings

There was no key statistical issue noted in this application, except a minor issue of how ANCOVA models were used to analyze the data. In analyzing the main co-primary endpoint of change in IIEF score, sponsor's statistical model included baseline IIEF score as covariate and fixed effects of age, region and treatment, while in analyzing the other two co-primaries (SEP-2 and SEP-3 in study 12093) their model also included a statistically significant treatment by region interaction term. A significant interaction term is generally indicates the need for further exploratory analysis by the respective factor (in this case regional variability) in question and should not be included in the model while evaluating the overall treatment effect. However, the efficacy results of our analysis using main effect models with or without interaction term were

similar to those of sponsor's results. We performed further analysis by region to discern potential regional variability in efficacy.

2. INTRODUCTION

2.1 Overview

The sponsor, Bayer HealthCare Pharmaceutical Inc, is seeking approval of Staxyn (Vardenafil orodispersible tablet 10 mg), in a rapid dissolution dosage form for the treatment of erectile dysfunction (ED). Vardenafil doses of 2.5, 5, 10, and 20 mg film-coated tablets were approved on August 18, 2003 in the US and are currently marketed as LEVITRA[®] for an oral treatment of ED. The rapid dissolution dosage form of Staxyn contains equivalent contents to the marketed 10 mg of Vardenafil. Staxyn can be disintegrated rapidly in mouth without water.

In support of the efficacy and safety of Staxyn, clinical data from two identical but separately designed Phase 3 studies (12093/A44851, 12094/A45684) were submitted. This review will focus on the efficacy data from the two Phase 3 studies listed in Table 2.1.

Table 2.1 Summary of Phase 3 Studies							
Study	Study site (number)	Study Design	Study Regimen/Number of Subjects		Duration of Treatment		
12093 (A44851)	Belgium (4) France (8) Germany (9) Spain (3) S. Africa (11) Netherlands (5)	Multi-center, Randomized, Double-blind, Placebo controlled.	Total Randomized: 362		12 weeks		
			<65 Years			≥65 Year	
			Placebo	Staxyn		Placebo	Staxyn
			82	88		94	98
12094 (A45684)	US (20) Mexico (5) Canada (4) Australia (6)	Multi-center, Randomized, Double-blind, Placebo controlled.	Total Randomized: 339		12 weeks		
			<65 Years			≥65 Year	
			Placebo	Staxyn		Placebo	Staxyn
			85	86		82	86

2.2 Data Sources

The study report and additional information were submitted electronically. The data quality of the submission was within the acceptable limit. Analysis datasets and associated definition files were listed in Table 2.2.

Table 2.2 Data Sources

Study	File	Location
12093 (A44851)	Datasets	\\CDSESUB1\EVSPROD\NDA200179\0000\m5\datasets\study-report-a44851\analysis\
	Definition	\\CDSESUB1\EVSPROD\NDA200179\0000\m5\datasets\study-report-a44851\analysis\define.pdf
12094 (A45684)	Datasets	\\CDSESUB1\EVSPROD\NDA200179\0000\m5\datasets\study-report-a45684\analysis\
	Definition	\\CDSESUB1\EVSPROD\NDA200179\0000\m5\datasets\study-report-a45684\analysis\define.pdf

2.3 Indication

Staxyn is indicated for the treatment of erectile dysfunction in men.

3. STATISTICAL EVALUATION

3.1 Overview of Study 12093 and Study 12094

3.1.1 Design and objectives

Design: The study design and the objectives of both studies were identical. Both studies were randomized, double-blind, multi-center, parallel-group, and placebo controlled. The sponsor's plan was to enroll 350 men of 18 years-of-age or older with ED for more than 6 months, stratified by age: <65 years and \geq 65 years. Study 12093 was conducted in Europe across 40 centers: Belgium (4), France (8), Germany (9), Spain (3), S. Africa (11), and Netherlands (5). Study 12094 was conducted across 35 centers: US (20), Canada (4), Mexico (5) and Australia (6). The primary objective of both studies was to compare the efficacy and safety of Staxyn after 12 weeks of treatment with placebo.

Both studies had duration of about 16 weeks, which included a 4-week non-medicated run-in period followed by a 12-week treatment period. At the end of the run-in period, eligible subjects were randomized in a 1:1 ratio to one of the two treatment groups, Staxyn and matching placebo. The randomization was stratified by age in order to obtain 50% of the subjects across two age strata. The follow-up period included 48 hours after the last intake of study medication.

Treatment compliance was defined as the total number of days that a tablet was taken divided by the study medication duration. The study duration was defined as the time between the day of first drug administration as recorded in the diary and the day of last drug administration, as determined by the end of study medication page.

Primary Efficacy Outcomes: The following three co-primary efficacy variables: erectile function score (IIEF-EF), successful penetration (SEP-2) and maintenance of erection (SEP-3) were evaluated in both studies.

The IIEF-EF score was the sum of the following IIEF Questions:

- IIEF01: Over the past 4 weeks, how often were you able to get an erection during sexual activity?

- IIEF02: Over the past 4 weeks, when you had erections with sexual stimulate on, how often were your erections hard enough for penetrate on?
- IIEF03: Over the past 4 weeks, when you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
- IIEF04: Over the past 4 weeks, during sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
- IIEF05: Over the past 4 weeks, during sexual intercourse, how difficult was it to maintain your erection to completion n of intercourse?
- IIEF15: Over the past 4 weeks, how would you rate your confidence that you could get and keep an erection?

Each of the above questions was rated from 0 to 5, with 0 meaning no improvement to 5 meaning most improvement.

The SEP-2 question was “Were you able to insert your penis into your partner’s vagina?” with Yes/No response. Similarly, the SEP-3 question was “Did your erection last long enough for you to have successful l intercourse?” with yes/no response. The overall success rate was defined as the percentage of “Yes” during the entire treatment course.

Secondary Efficacy Outcomes: Secondary efficacy parameters were also the same in both studies.

- Percentage of subjects achieving “back to normal” erectile function (IIEF-EF \geq 26) at Week 12
- All diary questions other than SEP-2 and SEP-3 concerning erectile function were assessed over the entire treatment period.
- Number of sexual attempts under medication till first successful attempt (SEP-3).
- The Treatment Satisfaction Scale (TSS); to be administered at the randomization visit and the final visit (or at Premature Discontinuation)
- A Global Assessment Question (GAQ) to be administered at the final visit only (or at Premature Discontinuation).

Safety Endpoints: In both studies, assessment of safety endpoints included the following:

- Blood and urine samples for routine hematology, serum chemistry, and semi-quantitative urinary dipstick testing
- Complete physical examination
- 12-lead ECG
- Vital signs
- Collection of adverse events data

Determination of Sample Size: Assuming a treatment difference of 4 points with standard deviation (SD) of 7.5 points for IIEF-EF, and 15% success rate for SEP-2 and SEP-3 with a common SD of 30%, 112 subjects per treatment group were adequate to provide 98% power for IIEF-EF or 96% power for SEP-2/ and SEP-3. Adjusting for 20% on-treatment non-response and drop outs, the final sample size was 175 subjects per treatment group, for a total of 350 subjects in each study.

Definition of Analysis Sets (Population): The intention-to-treat (ITT) population included all subjects who had taken at least one dose of study medication and who had baseline and any post-baseline efficacy data. The per-protocol (PP) population included all subjects who were belonged to the ITT population and had at least 12 weeks of treatment and measurements up to Week 12 for the IIEF-EF, the SEP-2, and the SEP-3, and who had no major protocol violation. The safety population included all randomized subjects with at least one drug application and one safety follow-up.

Handling of Missing Data: The post-baseline efficacy data was imputed using the last observation carried forward (LOCF) method. For the IIEF-EF score, it was set to missing if 2 or more questions were missing. If only one answer was missing, the IIEF-EF score was imputed by the average of the other five scores. For a missing answer to SEP-2/SEP-3, it was imputed as “NO” if the answer was “NO” to the question of “Were you able to achieve at least some erection (some enlargement of the penis)?”

Pooling of Sites: The blinded Review Committee (BRM) would decide the appropriate clustering of the centers/countries in case of unbalanced sample size/messy data.

Statistical Methods: The three co-primary variables were the baseline adjusted IIEF-EF at Week 12 and the baseline adjusted cumulative success rates in the SEP 2 (‘penetration’) and the SEP 3 (‘maintenance’) up to Week 12 or last observation. The statistical analysis of the IIEF-EF, the SEP-2, and the SEP-3 were conducted via three ANCOVA models as follows:

- Main effects (treatment, age, and center) plus baseline as a covariate plus baseline by treatment interaction
- Main effects (treatment, age, and center) plus baseline as covariate
- Main effects (treatment, age, and center) plus baseline as covariate plus center by treatment interaction

The interaction effect of age by treatment was neglected because pooled data analyses of previous studies never delivered significant interactions.

If baseline-by-treatment interaction was statistically significant ($p < 0.05$), differences between baseline and the dependent variable were selected and the baseline was dropped from the general linear model (GLM). If center-by-treatment interaction was found to be insignificant ($p > 0.1$), it would be excluded from the model.

The primary statistical analysis was based on both ITT and per protocol (completers) datasets. For secondary efficacy variables, the statistical analyses were performed only on the ITT sets. Categorical efficacy variables were analyzed by the Cochran-Mantel-Haenszel test (CMH) controlling for 'age' and 'center'. All other continuous efficacy variables were performed by the same models used in the primary efficacy analysis.

The efficacy would be demonstrated if all three co-primary efficacy variables were simultaneously statistically significant ($p < 0.05$) in favor of Staxyn.

Multiple Comparisons/Multiplicity: There was no need to adjust for multiplicity, since all three co-primary efficacy variables had to be statistically significant at nominal p-value of 0.05.

3.1.1 Reviewer's Comments on the Design

The statistical methods used for analyzing efficacy endpoints were appropriate except that the sponsor also included a significant interaction term (treatment by region) in the ANCOVA model while evaluating the overall treatment effect. For evaluating overall treatment effect, a main effect model is more than adequate and generally interaction terms are excluded from the model. Results of our analyses with or without significant interaction term were similar to sponsor's results. We, however, performed additional analyses based on significant interaction of treatment by region to discern any potential variation in results across (regions) different countries.

3.2 Results: Studies 12093 and 12094

3.2.1 Subject Disposition

In Study 12093, a total of 362 subjects (170 aged < 65 and 192 aged ≥ 65) were randomized to two treatment groups across 40 centers in Europe and Africa (Germany, France, Spain, Netherlands, Belgium, and South Africa). For analysis, sites were clustered together by country and countries were called ‘center’: Nine percent of the subjects discontinued the study prematurely, mostly due to lack of efficacy and voluntary withdrawal. The Intent-to-treat (ITT) dataset includes 355 subjects, greater than the planned sample size of 350.

In Study 12094, a total of 339 subjects (171 aged < 65 and 168 aged ≥ 65), were randomized to two treatment groups across 35 centers in North America and Australia. For analysis, sites were clustered together by country and countries were called ‘center’ such as Western USA, Eastern USA and Canada, Mexico, and Australia. Thirteen percent of the subjects prematurely discontinued from the study, mostly due to lack of efficacy and voluntary withdrawals. The ITT dataset includes 331 subjects, less than planned sample size of 350.

Category	Study 12093			Study 12094		
	Placebo	Staxyn	Total	Placebo	Staxyn	Total
Total Randomized	176	186	362	167	172	339
Completed Study	157 (89%)	173 (93%)	330 (91%)	144 (86%)	151(88%)	295 (87%)
Discontinued Study:	19 (11%)	13 (7%)	32 (9%)	23 (14%)	21 (12%)	44 (13%)
Adverse event	1 (1%)	3 (2%)	4 (1%)	1 (1%)	4 (2%)	5 (1%)
Consent withdrawn	7 (4%)	5 (3%)	12 (3%)	4 (2%)	6 (3%)	10 (3%)
Lack of Efficacy	8 (5%)	2 (1%)	10 (3%)	12 (7%)	2 (1%)	14 (4%)
Lost to follow-up	1 (1%)	2 (1%)	3 (1%)	3 (2%)	4 (2%)	7 (2%)
Others	2 (1%)	1 (1%)	3 (1%)	3 (2%)	5 (3%)	8 (2%)
ITT Analysis Set	172	183	355	162	169	331
Per Protocol Set	146	165	311	145	149	294

Source: Tables 10-1, 10-2, 10-3

Details of subject disposition by age were display in appendix Table 3.

3.2.2 Patient Demographics and Baseline Characteristics

The baseline characteristics such as age, race and body mass index (BMI) were similar across age groups (age <65 or ≥ 65) and treatment groups in both studies (Table 3.2.2). The main baseline values for IIEF-EF, SEP 2 and SEP 3 were also similar between the two treatment groups. Disposition by two age strata are shown in appendix Table 4.

Demographic Variable	Study 12093			Study 12094		
	Placebo	Staxyn	Total	Placebo	Staxyn	Total
Number of ITT Subjects	172	183	355	162	169	331
Mean Age (SD)	62.0 (10.78)	61.8 (10.96)	61.9 (10.88)	62.0 (10.84)	61.3 (11.37)	61.7 (11.11)
Body Mass Index (SD)	27.5 (3.98)	27.2 (3.38)	27.3 (3.68)	28.7 (4.26)	28.9 (4.39)	28.8 (4.32)
Weight (kg) (SD)	85.2 (13.67)	84.2 (11.88)	84.7 (12.77)	88.0 (14.66)	87.9 (15.78)	88.0 (15.21)
Race:						
White	116 (67.4%)	123 (67.2%)	239 (67.3%)	112 (69.1%)	117 (69.2%)	229 (69.2%)
Black	6 (3.5%)	7 (3.8%)	13 (3.7%)	9 (5.6%)	8 (4.7%)	17 (5.1%)
Asian	4 (2.3%)	8 (4.4%)	12 (3.4%)	3 (1.9%)	10 (5.9%)	13 (3.9%)
Hispanic	0 (0.0%)	0 (0.0%)	0 (0.0%)	37 (22.8%)	34 (20.1%)	71 (21.5%)
Other/Missing	46 (22.7%)	45 (24.5%)	91 (25.6%)	1 (0.6%)	0 (0%)	1 (0.3%)
ED Measurement at Baseline:						
IIEF-EF (SD)	12.8 (5.14)	12.8 (4.85)	12.8 (4.99)	12.9 (5.75)	11.8 (5.72)	12.4 (5.75)
SEP 2 (SD)	37.5 (36.04)	39.2 (35.50)	38.3 (35.72)	39.2 (35.10)	37.2 (36.20)	38.2 (35.63)
SEP 3 (SD)	14.4 (20.80)	13.3 (20.52)	13.8 (20.63)	15.5 (20.94)	12.9 (18.89)	14.1 (19.93)

Source: Reviewer's analysis on datasets STATCALC, PATINFO and VITALSV

3.2.3 Primary Efficacy Endpoints

As per protocol, the three following co-primary endpoints were evaluated to demonstrate efficacy:

- Change from baseline to week 12 in IIEF-EF Domain score.
- Change from baseline to week 12 in the success rates of penetration (SEP-2)
- Change from baseline to week 12 in the maintenance of erection (SEP-3)

Table 3.2.3.1 and 3.2.3.2 show the baseline mean and the mean change from baseline in all three co-primary endpoints at week 12 based on ANCOVA model. For evaluating the overall treatment effect, our analysis was based on the main effect model that included baseline, region, age group and treatment as opposed to sponsor's model that also included the interaction term of treatment by region. A significant interaction would indicate further evaluation of the effect size by region separately, and should not be included in the assessment of overall efficacy.

In both studies, the mean change in IIEF for Staxyn treated subjects was statistically significantly higher compared with subjects treated with placebo. Similarly, success rate for penetration and maintenance of erection was significantly higher for Staxyn subjects compared with placebo subjects.

The statistical inferences were consistent between the results of our main effect model and the sponsor's model with the interaction term.

Table 3.2.3.1 Mean (LS) Change from Baseline to Week 12 in Efficacy Endpoints: ITT Population				
Efficacy Endpoints	Statistics	Study 12093		
		Placebo (N=172)	Staxyn (N=183)	Difference (P-Value)^a
IIEF-EF	Baseline (SD)	12.8 (5.14)	12.8 (4.85)	7.11 (<.0001)
	Change from Baseline	1.59	8.70	
SEP 2	Baseline (SD)	37.5 (36.04)	39.4 (35.48)	29.05 (<.0001)
	Change from Baseline	6.88	35.94	
SEP 3	Baseline (SD)	14.5 (20.86)	13.2 (20.56)	39.97 (<.0001)
	Change from Baseline	11.63	51.61	

Source: Reviewer's analysis
a: p-value from main effect model: baseline +region +age group +treatment

Table 3.2.3.2 Mean (LS) Change from Baseline to Week 12 in Efficacy Endpoints: ITT Population				
Efficacy Endpoints	Statistics	Study 12094		
		Placebo (N=162)	Staxyn (N=169)	Difference (P-Value)^a
IIEF-EF	Baseline (SD)	12.9 (5.75)	11.8 (5.72)	6.92 (<.0001)
	Change from Baseline	1.53	8.45	
SEP 2	Baseline (SD)	39.2 (35.10)	37.2 (36.20)	25.97 (<.0001)
	Change from Baseline	4.82	30.80	
SEP 3	Baseline (SD)	15.5 (20.94)	12.9 (18.89)	33.43 (<.0001)
	Change from Baseline	12.44	45.87	

Source: Reviewer's analysis
a: p-value from main effect model: baseline +region +age group +treatment

3.2.4 Secondary Efficacy Endpoints

No secondary efficacy variables were reviewed.

3.2.5 Adjustment for Multiple Comparisons/Multiplicity

There was no adjustment for multiplicity for the three co-primary endpoints, since all three endpoints had to be statistically significant at nominal p-value of 0.05.

3.2.6 Reviewer's Comments on the Efficacy Results

Both studies were adequate with regards to design and analysis. The overall increase in IIEF-EF scores, the success rates of penetration (SEP2) and maintenance (SEP3) were statistically significant in the Staxyn group compared to the placebo group in both studies. Results were similar across countries, except in South Africa, where no statistically significant differences were noted with respect to SEP-2 and SEP-3 scores, mostly due to high placebo responses.

3.3 Evaluation of Safety

The evaluation of safety was referred to the medical review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age and Region

Age subgroup effect was not observed although the younger group tended to have better overall (combined placebo and Staxyn) improvement than the older group as shown in table 4.1. Within each age group, the improvements at Week 12 in the three co-primary endpoints were all statistically significant higher in the Staxyn group compared to the placebo group. More descriptive statistics were displayed in appendix Tables 1-2.

Region subgroup effect was observed for SEP-2 and SEP-3 in Study 12093 as shown in Table 4.2. In the region of South African, the improvement of the SEP-2 was not very clear mainly due to the very high placebo effect and small sample size (n=61).

No statistically significant treatment-by-region effect was found in Study 12094 although the region showed statistically significant effect for both SEP-2 and SEP-3 in the main effect model for Study 12094. Both co-primaries (SEP-2 and SEP-3) were statistically significant, regardless of varied placebo responses across regions as shown in Table 4.3.

4.2 Other Special/Subgroup Populations

Subgroup effects were also not observed in the subjects with diabetes, dyslipidemia, or hypertension in both studies.

4.3 Reviewer comments on subgroup analysis

Results of subgroups analyses are not powered to draw any meaningful statistical conclusion, mainly due to small sample sizes. Overall, there appear to be no regional variation with regards to efficacy, except in South Africa where Staxyn appear to be less efficacious.

Table 4.1 Efficacy Results by Age (LS Mean Change from Baseline, ITT & LOCF)							
Statistics		Study 12093			Study 12094		
		Placebo (N=172)	Staxyn (N=183)	P-Value	Placebo (N=162)	Staxyn (N=169)	P-Value
IIEF-EF	Age<65	2.35	9.93	<.0001 ^a	1.94	10.36	<.0001 ^a
	Age≥65	0.80	7.50	<.0001 ^a	1.12	6.54	<.0001 ^a
SEP 2	Age<65	7.9	38.9	<.0001 ^a	7.52	35.76	<.0001 ^a
	Age≥65	5.8	33.0	<.0001 ^a	2.15	25.84	<.0001 ^a
SEP 3	Age<65	15.4	55.2	<.0001 ^a	15.58	53.58	<.0001 ^a
	Age≥65	7.9	48.0	<.0001 ^a	9.39	38.15	<.0001 ^a

Source: Reviewer's analysis
a: p-value from the model: baseline +region +age group +treatment +age group*treatment

Table 4.2 Efficacy Results by region: Study 12093 (LS Mean Change from Baseline, ITT & LOCF)			
Statistics	Placebo (N=172)	Staxyn (N=183)	LS Mean Difference (P-Value)
IIEF-EF (n=353)	1.59	8.70	<.0001 ^a
SEP 2:			
France +Spain (n=89)	1.79	31.46	<.0001 ^b
Germany (n=104)	4.31	41.75	<.0001 ^b
Netherlands +Belgium (n=94)	7.96	39.55	<.0001 ^b
South Africa (n=61)	18.83	28.31	0.2333 ^b
SEP 3:			
France +Spain (n=88)	9.02	51.49	<.0001 ^b
Germany (n=102)	9.75	55.50	<.0001 ^b
Netherlands +Belgium (n=91)	10.12	53.77	<.0001 ^b
South Africa (n=61)	22.45	43.36	0.0105 ^b

Source: Reviewer's analysis
a: p-value from main effect model: baseline +region +age group +treatment
b: p-value from the model: baseline +region +age group +treatment +treatment*region

Table 4.3 Efficacy Results by region: Study 12094 (LS Mean Change from Baseline, ITT & LOCF)			
Statistics	Placebo (N=162)	Staxyn (N=169)	LS Mean Difference (P-Value)
IIEF-EF (n=327)	1.5	8.4	<.0001 ^a
SEP 2:			
Australia (n=74)	-1.9	27.6	<.0001 ^b
Eastern USA + Canada (n=89)	2.2	28.1	0.0001 ^b
Mexico (n=61)	14.6	42.1	0.0006 ^b
Western USA (n=105)	3.7	26.4	0.0002 ^b
SEP 3:			
Australia (n=74)	3.6	38.0	<.0001 ^b
Eastern USA + Canada (n=89)	9.9	46.5	<.0001 ^b
Mexico (n=61)	19.2	54.5	<.0001 ^b
Western USA (n=104)	16.4	45.3	<.0001 ^b

Source: Reviewer's analysis
a: p-value from main effect model: baseline +region +age group +treatment
b: p-value from the model: baseline +region +age group +treatment +treatment*region

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

No major statistical issues were noted in the sponsor's efficacy analysis. Our statistical analyses were based on main effect ANCOVA models as opposed to sponsor's use of models with both main effects and region by interaction term. In the evaluation of overall treatment effect, the statistical model should not include a significant interaction term. Our evaluation included further analysis of efficacy by region. The overall treatment effect, nevertheless, was consistently similar between our analysis and sponsor's analysis.

In regard to regional analysis, we find that the treatment difference for SEP-2 and SEP-3 in South Africa, were smaller than the other three regions mainly due to high placebo effect in South Africa. However, the overall results in both studies support the efficacy of Staxyn in the treatment of men with ED. Minor errors in the calculation of the overall SEP-2 and SEP-3 did not affect the statistical inferences drawn from both studies.

5.2 Conclusions and Recommendations

Data from the two Phase 3 studies demonstrated the efficacy of Staxyn in the treatment of erectile dysfunction in men. Staxyn statistically significantly increased the IIEF-EF score, and success rates in regard to both penetration (SEP-2) and maintenance of erection (SEP-3) at Week 12.

6. APPENDICES: Descriptive Statistics by Age Subgroup

Appendix Table 1. Absolute Values of Primary Efficacy Endpoints at Week 12 ITT population, LOCF								
Co-primary endpoint	Study 12093				Study 12094			
	Age < 65		Age ≥ 65		Age < 65		Age ≥ 65	
	Placebo	Staxyn	Placebo	Staxyn	Placebo	Staxyn	Placebo	Staxyn
Number of ITT Subjects	80	86	92	97	81	85	81	84
HEF-EF (SD)	15.44 (7.64)	23.05 (6.95)	13.15 (7.42)	19.92 (8.81)	14.99 (7.58)	22.95 (8.43)	13.58 (7.82)	17.79 (9.08)
SEP 2 (SD)	48.58 (39.55)	80.46 (26.84)	41.23 (37.22)	69.83 (35.87)	48.76 (38.83)	76.09 (33.85)	37.14 (37.18)	58.86 (39.33)
SEP 3 (SD)	29.71 (35.05)	70.77 (33.33)	22.27 (28.81)	59.97 (38.63)	30.71 (33.33)	69.55 (35.27)	24.26 (31.47)	48.07 (39.81)

Source: Reviewer's analysis

Appendix Table 2: Change from Baseline of Primary Efficacy Endpoints at Week 12 ITT population, LOCF								
Co-primary endpoint	Study 12093				Study 12094			
	Age < 65		Age ≥ 65		Age < 65		Age ≥ 65	
	Placebo	Staxyn	Placebo	Staxyn	Placebo	Staxyn	Placebo	Staxyn
Number of ITT Subjects	80	86	92	97	81	85	81	84
HEF-EF (SD)	2.08 (7.33)	9.62 (6.28)	0.89 (6.42)	7.68 (8.19)	1.73 (6.28)	10.33 (7.78)	1.05 (6.01)	6.71 (8.06)
SEP 2 (SD)	5.51 (42.82)	35.78 (33.63)	8.72 (28.41)	34.55 (38.95)	4.56 (34.12)	33.16 (33.27)	3.04 (33.33)	27.29 (37.39)
SEP 3 (SD)	15.19 (31.30)	54.45 (32.72)	7.71 (25.72)	49.21 (37.28)	15.22 (29.55)	53.15 (33.22)	8.74 (29.15)	38.76 (38.32)

Source: Reviewer's analysis

Appendix Table 3: Disposition of Subjects of Studies 12093 and 12094 by Age										
Category	Study 12093					Study 12094				
	Age < 65		Age ≥ 65		Total	Age < 65		Age ≥ 65		Total
	Placebo	Staxyn	Placebo	Staxyn		Placebo	Staxyn	Placebo	Staxyn	
Total Randomized	82	88	94	98	362	85	86	82	86	339
Completed Study	75 (91%)	80 (91%)	82 (87%)	93 (95%)	330 (91%)	72 (85%)	75 (87%)	72 (88%)	76 (88%)	295 (87%)
Discontinued Study	7 (9%)	8 (9%)	12 (13%)	5 (5%)	32 (9%)	13 (15%)	11 (13%)	10 (12%)	10 (12%)	44 (13%)
Adverse event	0 (0%)	1 (1%)	1 (1%)	2 (2%)	4 (1%)	0 (0%)	3 (3%)	1 (1%)	1 (1%)	5 (1%)
Consent withdrawn	4 (5%)	4 (5%)	3 (3%)	1 (1%)	12 (3%)	3 (4%)	3 (3%)	1 (1%)	3 (3%)	10 (3%)
Lack of Efficacy	2 (2%)	1 (1%)	6 (6%)	1 (1%)	10 (3%)	5 (6%)	2 (2%)	7 (9%)	0 (0%)	14 (4%)
Lost to follow-up	0 (0%)	2 (2%)	1 (1%)	0 (0%)	3 (1%)	2 (2%)	2 (2%)	1 (1%)	2 (2%)	7 (2%)
Others	1 (1%)	0 (0%)	1 (1%)	1 (1%)	3 (1%)	3 (4%)	1 (1%)	0 (0%)	4 (5%)	8 (2%)
ITT Analysis Set	80	86	92	97	355	81	85	81	84	331
Per Protocol Set	70	76	76	89	311	69	75	76	74	294

Source: Tables 10-1, 10-2, 10-3

Appendix Table 4: Subject Demographic and Baseline Characteristics (ITT) by Age									
Demographic Variable	Study 12093				Study 12094				
	Age < 65		Age ≥ 65		Age < 65		Age ≥ 65		
	Placebo	Staxyn	Placebo	Staxyn	Placebo	Staxyn	Placebo	Staxyn	Staxyn
Number of ITT Subjects	80	86	92	97	81	85	81	84	84
Mean Age (SD)	52.9 (8.2)	52.8 (9.1)	69.9 (4.9)	69.7 (4.2)	53.5 (7.8)	52.4 (8.7)	70.6 (5.3)	70.3 (4.9)	70.3 (4.9)
Body Mass Index (SD)	28.0 (4.3)	27.5 (3.5)	27.1 (3.6)	26.9 (3.2)	28.7 (4.4)	29.1 (5.0)	28.7 (4.1)	28.7 (3.7)	28.7 (3.7)
Weight (kg) (SD)	88.2 (14.9)	87.1 (11.8)	82.6 (11.9)	81.6 (11.4)	88.5 (15.1)	89.6 (17.0)	87.5 (14.2)	86.2 (14.3)	86.2 (14.3)
Race:									
White	52 (65.0%)	55 (64.0%)	64 (69.6%)	68 (70.1%)	52 (64.2%)	53 (62.4%)	60 (74.1%)	64 (76.2%)	64 (76.2%)
Black	2 (2.5%)	3 (3.5%)	4 (4.4%)	4 (4.1%)	7 (8.6)	7 (8.2%)	2 (2.5%)	1 (1.2%)	1 (1.2%)
Asian	2 (2.5%)	5 (5.8%)	2 (2.2%)	3(3.1%)	2 (2.5%)	6 (7.1%)	1 (1.2%)	4 (4.8%)	4 (4.8%)
Hispanic	0 (0%)	0 (0%)	0 (0%)	0 (0%)	20 (24.7%)	19 (22.4%)	17 (21.0%)	15 (17.9%)	15 (17.9%)
Other/Missing	24 (30.0%)	23 (26.7%)	22 (23.9%)	22 (22.7%)	0 (0%)	0 (0%)	1 (1.2%)	0 (0%)	0 (0%)
ED Measurement at Baseline:									
HIEF-EF (SD)	13.4 (4.7)	13.4 (4.8)	12.3 (5.4)	12.2 (4.9)	13.3 (5.1)	12.6 (5.6)	12.5 (6.4)	11.1 (5.8)	11.1 (5.8)
SEP 2 (SD)	43.1 (36.9)	44.7 (36.7)	32.5 (34.8)	34.3 (33.9)	44.2 (33.5)	42.9 (35.6)	34.1 (36.1)	31.6 (36.1)	31.6 (36.1)
SEP 3 (SD)	14.5 (21.6)	16.3(22.0)	14.2 (20.1)	10.6 (18.8)	15.5 (19.7)	16.4 (18.7)	15.5 (22.3)	9.3 (18.5)	9.3 (18.5)

Source: Reviewer's analysis on datasets PATINFO and VITALSV

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-200179	ORIG-1	BAYER HEALTHCARE PHARMACEUTICALS INC	VARDENAFIL HCL

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/s/

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