Drug product:	SEROQUEL XR	**SYNOPSIS**	
Drug substance(s):	quetiapine fumarate extended release		
Edition No.:	Final		
Study code:	D1448C00007		
Date:	20 November 2007		

A Multicenter, Double-blind, Randomized, Parallel-group, Placebo-controlled Phase III Study of the Efficacy and Safety of Quetiapine Fumarate Extended-release (SEROQUEL XR™) in Combination with an Antidepressant in the Treatment of Patients with Major Depressive Disorder with Inadequate Response to an Antidepressant Treatment (Onyx Study)

Study center(s)

Five hundred seventy-two patients were enrolled to obtain 493 patients assigned to randomized treatment in Europe, South Africa, North America, and Australia to yield 420 evaluable patients at 87 study sites.

Publications

None at the time of the writing of this report.

Study dates		**Phase of development**
First patient enrolled	8 May 2006	Therapeutic confirmatory (III)
Last patient completed	7 April 2007	

Objectives

The **primary** objective of the study was to evaluate the efficacy of quetiapine fumarate extended-release (in combination with an antidepressant versus an antidepressant in combination with placebo in patients with Major Depressive Disorder (MDD).

Hereafter, quetiapine fumarate extended-release will be referred to as quetiapine XR (note that quetiapine fumarate extended-release was previously referred to as quetiapine fumarate sustained-release).

The **secondary** objectives were:

1. To evaluate if quetiapine XR in combination with an antidepressant improves health-related quality of life of patients with MDD, compared to an antidepressant in combination with placebo;

2. To evaluate if quetiapine XR in combination with an antidepressant reduces anxiety symptoms in patients with MDD, compared to an antidepressant in combination with placebo;

3. To evaluate if quetiapine XR in combination with an antidepressant improves sleep quality in patients with MDD, compared to an antidepressant in combination with placebo;

4. To evaluate if quetiapine XR in combination with an antidepressant is effective in reducing suicidal ideation in patients with MDD, compared to an antidepressant in combination with placebo;

5. To evaluate if quetiapine XR in combination with an antidepressant improves somatic symptoms in patients with MDD, compared to an antidepressant in combination with placebo;

6. To evaluate if quetiapine XR in combination with an antidepressant improves satisfaction with medication in patients with MDD, compared to an antidepressant in combination with placebo;

7. To evaluate if quetiapine XR in combination with an antidepressant is as safe and well-tolerated as an antidepressant in combination with placebo in the treatment of patients with MDD;

8. To evaluate if quetiapine XR in combination with an antidepressant changes the plasma level of antidepressant.

An additional objective was to establish a panel of DNA samples from patients who provided separate consent for genetic research in order to enable exploratory studies of genetic factors that may influence drug response. The genetic research was optional for individual patients and centers and is not accounted for in this study report.

Study design

This was a 6-week, multicenter, double-blind, randomized, parallel-group, placebo-controlled, double-dummy, phase III study of the efficacy and safety of quetiapine XR 150 mg/day and 300 mg/day in combination with an antidepressant in the treatment of patients with MDD who have shown an inadequate response to an antidepressant treatment. The randomized treatment period was preceded by a washout period of up to 14 days. Patients continued to maintain the same antidepressant therapy from the period beginning at enrollment through the end of double-blind treatment.

Target population and sample size

Male or female patients, 18 to 65 years old, inclusive, with a Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) diagnosis of MDD, Single Episode (296.2x) or MDD, Recurrent (296.3x) as confirmed by the Mini-International Neuropsychiatric Interview (MINI).

Patients should have been on treatment with 1 of the following antidepressants for at least 6 weeks prior to enrollment (at least minimum effective antidepressant dose according to label), with at least 1 dose increase when permitted according to label:

- amitriptyline, bupropion, citalopram, duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, or venlafaxine.

In addition, patients had to have a Hamilton Rating Scale for Depression (HAM-D) (17-item, hereafter referred to as HAM-D) total score ≥20 and a HAM-D Item 1 (depressed mood, hereafter referred to as HAM-D Item 1) score ≥2 at both enrollment and randomization.

It was planned to randomly assign 450 patients to obtain a total of 420 evaluable patients (140 per treatment group). The sample size calculation in this study was done to demonstrate superior efficacy of quetiapine XR over placebo in combination with an antidepressant with respect to the primary outcome variable, change in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score from randomization to Week 6. The planned sample size ensured a power of 90% and was attained by anticipating a difference of 3.5 units from placebo and a variability (standard deviation) of 9 for the change in the MADRS total score from randomization to Week 6.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

The eligible patients were randomly assigned to 1 of the 3 treatment arms: quetiapine XR 150 mg/day, quetiapine XR 300 mg/day, or placebo in combination with ongoing antidepressant treatment. Tablets used in the study were: 50-mg and 300-mg quetiapine XR tablets, placebo tablets to match the 50-mg and 300-mg quetiapine XR tablets, and 1 ongoing antidepressant treatment in combination with quetiapine XR or placebo. Quetiapine XR 50-mg and 300-mg tablets (or placebo to match) were administered orally once daily in the evening.

Study treatment was given in tablets of the following doses (lot #): quetiapine XR 50 mg (LJ4707, 41279H06, LM4625), quetiapine XR 300 mg (33419D05, 41280I06, LM4617), placebo 50-mg match (32195F05, 32200H05, 32201E05, 32202B05), and placebo 300-mg match (CP296X, CP297X).

Duration of treatment

Eligible patients underwent a washout period of up to 14 days for the discontinuation of all prohibited medications. Patients then entered a 6-week treatment period, when they were randomly assigned to blinded treatment in a 1:1:1 ratio to 150 mg/day quetiapine XR, 300 mg/day quetiapine XR, or placebo (each in combination with the ongoing antidepressant treatment). All quetiapine XR patients started on 50 mg/day, and were up-titrated to 150 mg/day on Day 3. Patients in the quetiapine XR 150 mg/day–group maintained this dose through the end of the randomized treatment period. Patients in the quetiapine XR 300 mg/day–group were up-titrated to 300 mg/day on Day 5, and then maintained this dose through the end of the randomized treatment period. The ongoing treatment with the antidepressant was maintained at the same dose throughout the study.

Criteria for evaluation (main variables)

The outcome variables are presented in Table S1.

Table S1 Outcome variables

Primary efficacy outcome variable
Change from randomization to Week 6 in the MADRS total score.
Secondary efficacy variables supporting the primary objective
Change from randomization to each assessment in MADRS total score; MADRS response, defined as a ≥50% reduction from randomization in the MADRS total score at Week 1 and Week 6; MADRS remission, defined as total score ≤8 at Week 6; change from randomization to Week 6 in the HAM-D total score and the HAM-D Item 1 score; change from randomization to Week 6 in the CGI-S score; the proportion of patients with CGI-I score of "much/very much improved" at Week 6.
Secondary variable of particular interest
Change from randomization to Week 6 in the Q-LES-Q percent maximum total score.
Other secondary efficacy variables
Change from randomization to Week 6 in the Q-LES-Q overall quality of life score, HAM-A total score, HAM-A psychic anxiety subscale score, HAM-D anxiety items score, HAM-D sleep disturbance items score, PSQI global score, MADRS Item 10 (suicidal thoughts) score, HAM-A somatic anxiety subscale score, and Q-LES-Q satisfaction with medication score.
Pharmacokinetics
Change from randomization to Week 2 and Week 4 in the plasma concentration of antidepressant.

Safety variables

Laboratory values, physical examination, vital signs, weight, BMI, waist circumference, ECG, SAS, BARS, CSFQ, AEs (including EPS-related), MADRS Item 10 score ≥4 or an AE of or related to suicidality, and suicidality analysis.

AE Adverse event. BARS Barnes Akathisia Rating Scale. CGI-I Clinical Global Impression - Improvement. CGI-S Clinical Global Impression - Severity. CSFQ Changes in Sexual Functioning Questionnaire. ECG Electrocardiogram. EPS Extrapyramidal symptoms. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. MADRS Montgomery-Åsberg Depression Rating Scale. PSQI Pittsburgh Sleep Quality Index. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. SAS Simpson-Angus Scale.

Statistical methods

All hypotheses were tested with 2-sided tests. Where appropriate, model-based point estimates were presented together with 2-sided 95% confidence intervals. Missing data were handled using the last observation carried forward (LOCF) approach, as appropriate.

The primary efficacy outcome variable (change in MADRS total score from baseline to Week 6) was analyzed using an analysis of covariance (ANCOVA) model that included baseline MADRS total score as covariate, treatment as fixed effect, and center as random effect. The secondary efficacy outcome variable of particular interest (change in Quality of Life Enjoyment Satisfaction Questionnaire [Q-LES-Q] total score from baseline to Week 6) was analyzed the same way as the primary variable. A step-wise sequential testing procedure was used for multiple comparisons across these 2 groups of efficacy variables to ensure that the overall significance level of 0.05 was preserved. First the change in MADRS total score from randomization to Week 6 was tested for each dose versus placebo. If both the quetiapine XR doses were statistically significantly better than placebo, then the change in the Q-LES-Q percent maximum total score from baseline to Week 6 was tested for each dose versus placebo. To handle multiplicity within each step, the Simes-Hommel procedure was used (Hommel 1988). No correction of multiplicity was applied for any other variables.

Changes from randomization to each assessment in the MADRS total score as well as changes from randomization to Week 6 in the HAM-D total scores, HAM-D Item 1 score, Clinical Global Impression - Severity (CGI-S) score, Hamilton Rating Scale for Anxiety (HAM-A) total score, HAM-A psychic anxiety subscale score, HAM-A somatic anxiety subscale score, and Pittsburgh Sleep Quality Index (PSQI) global score were analyzed similarly to the primary objective. The MADRS response at Week 1 and Week 6 and remission at Week 6, as well as the dichotomized Clinical Global Impression - Improvement (CGI-I) score ("much/very much improved" scores as 1 category versus all other scores as the second category) at Week 6 were analyzed utilizing logistic regression models. Changes from randomization to Week 6 in the MADRS Item 10 score, HAM-D anxiety items score, HAM-D sleep disturbance items score, Q-LES-Q overall quality of life (Item 16) score, Q-LES-Q satisfaction with medication (Item 15) score, changes from randomization to Weeks 2 and 4 in plasma concentration levels of antidepressants, as well as all safety assessments were presented by descriptive statistics.

The efficacy analyses were based on the modified intention-to-treat (MITT) analysis set (Full Analysis Set), and the safety analyses were done on the data from patients in the safety analysis set. The per-protocol (PP) analysis set included all patients in the MITT analysis set with no significant protocol violations or deviations.

Patient population

Analysis sets and patient baseline characteristics are presented in Table S2.

Table S2 Analysis sets and patient baseline characteristics

		PLA	QTP150	QTP300	Total
Analysis sets					
N (randomized)		163	167	163	493
N safety[a]		161	167	163	491
N MITT[b]		160	166	161	487
N PP		145	146	139	430
Completed study		145	146	133	424
Demographic characteristics (MITT analysis set)					
Sex: n (%)	Male	56 (35.0)	51 (30.7)	51 (31.7)	158 (32.4)
	Female	104 (65.0)	115 (69.3)	110 (68.3)	329 (67.6)
Age: years	Mean (SD)	44.8 (10.4)	46.0 (10.1)	45.5 (11.1)	45.4 (10.5)
	Min to max	20 to 64	21 to 65	18 to 65	18 to 65
Race: n (%)	Caucasian	157 (98.1)	165 (99.4)	156 (96.9)	478 (98.2)
	Black	2 (1.3)	0 (0.0)	2 (1.2)	4 (0.8)
	Oriental	1 (0.6)	0 (0.0)	1 (0.6)	2 (0.4)
	Other	0 (0.0)	1 (0.6)	2 (1.2)	3 (0.6)
Baseline disease characteristics (MITT analysis set)					
DSM-IV diagnosis: n (%)					
296.2x MDD, Single Episode		31 (19.4)	32 (19.3)	29 (18.0)	92 (18.9)
296.3x MDD, Recurrent		129 (80.6)	134 (80.7)	132 (82.0)	395 (81.1)
MADRS	Mean (SD)	28.2 (5.6)	28.6 (5.4)	28.4 (5.5)	NC
HAM-D	Mean (SD)	24.5 (3.38)	24.6 (3.00)	24.8 (3.19)	NC
HAM-D Item 1	Mean (SD)	2.9 (0.6)	2.8 (0.6)	2.9 (0.5)	NC
HAM-A	Mean (SD)	20.2 (5.9)	21.0 (6.4)	21.1 (6.0)	NC
CGI-S	Mean (SD)	4.6 (0.8)	4.6 (0.7)	4.7 (0.7)	NC

Table S2 Analysis sets and patient baseline characteristics

		PLA	QTP150	QTP300	Total
Q-LES-Q	Mean (SD)	41.0 (13.3)	39.3 (12.2)	40.6 (12.6)	NC

[a] Number of patients who received at least 1 dose of investigational product.
[b] Number of patients who took at least 1 dose of investigational product and had a randomization MADRS assessment and at least 1 valid MADRS assessment after randomization.
CGI-S Clinical Global Impression Severity scale. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. MADRS Montgomery-Åsberg Depression Rating Scale. MDD Major Depressive Disorder. MITT Modified intention-to-treat. n Number of patients. NC Not calculated. PLA Placebo. PP Per-protocol. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR. SD Standard deviation.

Efficacy results

The key efficacy results of the study are presented in Table S3.

Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)

Outcome variable	PLA N=160	QTP150 N=166	QTP300 N=161
MADRS total score, LS mean change from baseline	-12.21	-15.26[a]	-14.94[a]
Proportion with ≥50% MADRS response	46.3%	55.4%	57.8%[b]
Proportion with MADRS remission (total score ≤8)	23.8%	36.1%[b]	31.1%
HAM-D total score, LS mean change from baseline	-11.13	-13.81[c]	-13.56[a]
HAM-D Item 1 score, LS mean change from baseline	-1.35	-1.56	-1.57
HAM-A total score, LS mean change from baseline	-7.92	-10.27	-9.70
CGI-S score, LS mean change from baseline	-1.25	-1.72[c]	-1.64[b]
Proportion improved in CGI-I	52.5%	64.5%[b]	62.7%

Table S3 Efficacy results at Week 6 (LOCF, MITT analysis set)

Outcome variable	PLA N=160	QTP150 N=166	QTP300 N=161
Q-LES-Q % maximum total score, LS mean change from baseline	12.58	14.70	12.81

[a] p<0.01 comparison with placebo.
[b] p<0.05 comparison with placebo.
[c] p<0.001 comparison with placebo.

CGI-I Clinical Global Impression Improvement scale. CGI-S Clinical Global Impression Severity scale. HAM-A Hamilton Rating Scale for Anxiety. HAM-D Hamilton Rating Scale for Depression. LOCF Last observation carried forward. LS Least square. MADRS Montgomery-Åsberg Depression Rating Scale. MITT Modified intention-to-treat. PLA Placebo. Q-LES-Q Quality of Life Enjoyment Satisfaction Questionnaire. QTP Quetiapine XR.

Note: For the analyses of MADRS and Q-LES-Q change from baseline, p-values were adjusted and compared with α=0.05 using the Simes-Hommel procedure within the step-wise sequential testing strategy.

In patients with MDD, quetiapine XR at a dose of either 150 mg/day or 300 mg/day was statistically superior to placebo in reducing the level of depressive symptoms as demonstrated by the change from randomization to Week 6 in the MADRS total score. The treatment advantage for both doses of quetiapine XR was observed at Week 1 and was consistently observed through Week 6 as determined by the change in the MADRS total score over time, MADRS response rate, and CGI-I. Overall, results from the secondary outcome variables supported the primary objective. For example, both quetiapine XR groups demonstrated greater MADRS response, remission, and reduction in the HAM-A total score in comparison to the placebo group. However, in the evaluation of health-related quality of life (using the Q-LES-Q), no statistical significance was obtained between the two quetiapine XR groups and placebo.

There did not appear to be a consistent trend in the relative mean change from baseline in the plasma concentrations of the antidepressants and their associated metabolites in the presence of co-administered quetiapine XR that would indicate significant drug interactions requiring dose-adjustment of the antidepressant.

Safety results

The number (%) of patients who had at least 1 adverse event (AE) in any category is summarized in Table S4. Both the 150-mg/day and 300-mg/day doses of quetiapine XR were generally well-tolerated. The overall incidence of AEs was highest in the quetiapine XR 300-mg/day group, followed by the quetiapine XR 150-mg/day and placebo groups. Most AEs were of mild to moderate severity in all treatment groups. Serious AEs (SAEs) were infrequent in all treatment groups. A larger proportion of patients in the quetiapine XR groups discontinued due to an AE compared to the placebo group. The incidence of AEs considered by the investigator to be possibly related to study medication was higher in the quetiapine XR treatment groups compared to placebo and, as with the discontinuations due to AEs, it appeared to be dose-related.

Table S4 Patients who had an adverse event in any category (safety analysis set)

Category of adverse event	PLA N=161 n (%)	QTP150 N=167 n (%)	QTP300 N=163 n (%)
Any adverse event	87 (54.0)	109 (65.3)	122 (74.8)
Serious adverse event	3 (1.9)	2 (1.2)	3 (1.8)
Serious adverse event leading to death	0	0	0
Drug-related adverse event[a]	40 (24.8)	83 (49.7)	107 (65.6)
Adverse events leading to discontinuation	6 (3.7)	11 (6.6)	19 (11.7)

[a] As judged by the investigator.
n Number of patients. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine XR.
Note: Patients with multiple events in the same category are counted only once.
Note: Percentages are calculated as n/N*100.

The incidence of common AEs (occurring at an incidence of ≥2% in any treatment group) is shown by preferred term in Table S5.

Table S5 Common (≥2%) adverse events by preferred term (safety analysis set)

MedDRA preferred term[a]	PLA N=161 n (%)	QTP150 N=167 n (%)	QTP300 N=163 n (%)
Dry mouth	11 (6.8)	34 (20.4)	58 (35.6)
Somnolence	5 (3.1)	28 (16.8)	38 (23.3)
Fatigue	5 (3.1)	22 (13.2)	24 (14.7)
Sedation	7 (4.3)	16 (9.6)	21 (12.9)
Constipation	6 (3.7)	7 (4.2)	17(10.4)
Dizziness	12 (7.5)	19 (11.4)	15 (9.2)
Headache	16 (9.9)	15 (9.0)	13 (8.0)
Nausea	10 (6.2)	9 (5.4)	9 (5.5)
Weight increased	0	7 (4.2)	7 (4.3)
Dyspepsia	2 (1.2)	4 (2.4)	6 (3.7)
Vertigo	2 (1.2)	5 (3.0)	6 (3.7)
Nasopharyngitis	10 (6.2)	5 (3.0)	5 (3.1)
Abdominal pain upper	2 (1.2)	4 (2.4)	4 (2.5)
Increased appetite	0	1 (0.6)	4 (2.5)

Table S5 Common (≥2%) adverse events by preferred term (safety analysis set)

MedDRA preferred term[a]	PLA N=161 n (%)	QTP150 N=167 n (%)	QTP300 N=163 n (%)
Back pain	3 (1.9)	5 (3.0)	3 (1.8)
Hyperhidrosis	7 (4.3)	2 (1.2)	3 (1.8)
Influenza	1 (0.6)	4 (2.4)	3 (1.8)
Insomnia	7 (4.3)	3 (1.8)	2 (1.2)
Lethargy	2 (1.2)	5 (3.0)	2 (1.2)
Vomiting	2 (1.2)	5 (3.0)	1 (0.6)

[a] Patients with multiple events falling under the same preferred term are counted only once in that term.
MedDRA Medical Dictionary of Regulatory Activities. n Number of patients. N Number of patients in treatment group. PLA Placebo. QTP Quetiapine XR.
Note: Common adverse event is defined as an event occurring at an incidence of ≥2% in any treatment group.
Note: Events sorted by decreasing frequency in the QTP300 treatment group.
Note: Percentages are calculated as n/N*100.

The pattern of common AEs observed in the quetiapine XR treatment groups generally conformed to that which was anticipated based on the known pharmacological profile of quetiapine. The most common AEs in the quetiapine XR groups were dry mouth, somnolence, fatigue, sedation, and dizziness, and occurred at a higher incidence compared to placebo.

The incidence of extrapyramidal symptoms (EPS)-related AEs in the quetiapine XR treatment groups was low (≤5%) with no dose-related pattern, and was generally comparable to placebo. All were of mild or moderate severity. The most common AEs potentially related to EPS were akathisia, restlessness, and tremor. Overall, the assessment of parkinsonian and akathisia symptoms as assessed by Simpson-Angus Scale (SAS) and Barnes Akathisia Rating Scale (BARS) scores indicated that quetiapine XR treatment was similar to placebo, and an improvement or no worsening in symptoms was noted in most patients in all active treatment groups at the end of treatment.

The incidence of AEs related to suicidality was low in all treatment groups. There was no clinical evidence to suggest a relationship between quetiapine XR treatment and increased suicidality. A higher percentage of patients in the placebo group had a MADRS suicidal thoughts (Item 10) score of ≥4 (at least at ≥1 time point after randomization).

A shift from normal to a clinically important low neutrophil count occurred in 1 patient in the placebo group and 2 patients in the quetiapine XR 150-mg/day group. One patient experienced an AE related to neutropenia (a patient in the quetiapine XR 150-mg/day group); the neutrophil level was normal at the end of treatment. There were no cases of agranulocytosis.

Overall, the clinical laboratory results were consistent with those from previous studies in patients treated with quetiapine for other disorders. There were no differences among the treatment groups in the changes from baseline that were judged to be clinically relevant for any hematology assessments. The most notable changes in clinical chemistry parameters were the increases in triglycerides and low-density lipoprotein (LDL) cholesterol in the 2 quetiapine XR groups compared to placebo, although there was a high degree of interpatient variability.

Mean insulin and glycated hemoglobin (HbA1c) values were increased from baseline in both quetiapine XR groups (eg, approximately 1.8 μIU/mL, and 0.05%, respectively). Glucose levels at the end of treatment were increased from baseline to a similar degree in the placebo and quetiapine XR 300-mg/day groups (eg, 1.9 and 2.0 mg/dL, respectively); levels were slightly decreased in the quetiapine XR 150-mg/day group (eg, -0.2 mg/dL). The incidence of potentially diabetes-related AEs was low and equally distributed among the placebo and quetiapine XR groups. The increases in glucose and insulin levels from baseline were not as pronounced when limited to patients who were confirmed to have been fasting for at least 8 hours prior to blood sampling. The incidence of patients with a treatment emergent shift from <3 to ≥3 metabolic risk factors was higher in the placebo group compared to the other 2 treatment groups (placebo: 10%, quetiapine XR 150 mg/day: 7%, and quetiapine XR 300 mg/day: 9%). There were no cases of treatment-emergent hypothyroidism based on clinically important high thyroid-stimulating hormone (TSH) values in combination with clinically important low thyroxine (T4) values; no AEs of hypothyroidism were reported. The incidences of shifts to clinically important high prolactin values were low and similar in all treatment groups (placebo: 2.0%, quetiapine XR 150 mg/day: 1.3%, and quetiapine XR 300 mg/day: 2.7%).

The percentages of patients with a ≥7% weight increase between baseline and the end of treatment was higher in both quetiapine XR groups compared to the placebo group (eg, 7% and 2%, respectively). Across all treatment groups including placebo, there was a trend for a weight gain of ≥7% to occur more often in patients in the lower body mass index (BMI) categories. A weight decrease of ≥7% between baseline and the end of treatment, the incidence of which was low, occurred more often in the placebo group compared to the quetiapine XR groups (eg, 3% and 0-1%, respectively).

A small increase in mean pulse rate, confirmed by electrocardiographic (ECG) measurement of heart rate, was observed in the quetiapine XR groups (mean, 1 bpm). Combined criteria for orthostatic changes in pulse and systolic blood pressure did not show any differential effect of quetiapine XR administration compared to placebo. No ECG changes judged to be clinically relevant were observed. No AEs potentially related to QT prolongation occurred during the study.

Based on the change from baseline to the end of treatment in the Changes in Sexual Functioning Questionnaire (CSFQ) total score, sexual functioning improved slightly in all 3 treatment groups.