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Effects of the Cannabinoid-1 Receptor Antagonist Rimonabant on Psychiatric Symptoms in Overweight People With Schizophrenia:

A Randomized, Double-Blind, Pilot Study

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Abstract

Weight gain is a major adverse effect of several second-generation antipsychotic medications. Rimonabant is a cannabinoid-1 receptor antagonist that promotes weight loss in the general population. We conducted a 16-week, double-blind, placebo-controlled study of rimonabant (20 mg/d) in people with schizophrenia or schizoaffective disorder, based on the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria, who were clinically stable on second-generation antipsychotics. Participants had a body mass index of 27 kg/m² or higher with hyperlipidemia or body mass index of 30 kg/m² or higher, and no current substance abuse/dependence (except nicotine), more than weekly cannabis use, or recent depressive symptoms/suicidality. An exercise and dietary counseling group was offered weekly. Target enrollment was 60; the trial was terminated early because of withdrawal of rimonabant from the European market. Fifteen participants were randomized (7 rimonabant, 8 placebo); 5 completed in each group. Rimonabant was associated with a greater reduction in Brief Psychiatric Rating Scale total score versus placebo (mean ± SE difference, -1.9 ± 0.8 , $P = 0.02$), driven by differences in the Brief Psychiatric Rating Scale anxiety/depression (-1.4 ± 0.35 , $P = 0.0004$) and hostility (-0.7 ± 0.3 , $P = 0.02$) factors. Group differences were not significant for the Calgary Depression Scale total score ($P = 0.24$), Scale for the Assessment of Negative Symptoms total score ($P = 0.13$), weight, blood pressure, or fasting lipids or glucose. Rimonabant was well tolerated with no significant adverse events. No significant weight loss, metabolic effects, or adverse psychiatric effects were associated with the cannabinoid-1 receptor antagonist rimonabant in this small sample of people

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AUTHOR DISCLOSURE INFORMATION

Deanna L. Kelly, David Gorelick, Douglas L. Boggs, Robert P. McMahon, Jared Linthicum, Fang Liu, Stephanie Feldman, M. Patricia Ball, Heidi J. Wehring, Stephen J. Heishman, and Kimberly Warren have no competing interests or financial support to disclose. Robert R. Conley is a fulltime employee and stockholder of Eli Lilly & Co. Marilyn A. Huestis has a cooperative research and development agreement with Sanofi-Aventis. Robert W. Buchanan is a member of the data and safety monitoring board of Cephalon, Otsuka, Pfizer, and Wyeth; a consultant for Abbott, GlaxoSmithKline, Merck, Organon, Sanofi-Aventis, Solvay, and Wyeth; and a member of the advisory board of AstraZeneca, Pfizer, and Roche.

with schizophrenia. The endocannabinoid system remains a promising target for pharmacotherapy of schizophrenia and obesity.

Keywords

rimonabant; schizophrenia; obesity; metabolic syndrome; depression

People with schizophrenia are at greater risk than the general population for developing obesity or obesity-related health disorders.¹ The estimated obesity prevalence is 40% to 60% in people with schizophrenia, compared with approximately 30% in the general population.^{2,3} The prevalence of metabolic syndrome is approximately 30% to 60%, compared with approximately 25% in the general population,^{4–6} and the prevalence of type 2 diabetes mellitus is approximately 2- to 3-fold higher, compared with the general population.^{4,7–9} The increased prevalence of these conditions likely contributes to the 5-fold increased mortality risk and shorter life expectancy (15 years) observed in people with schizophrenia.^{10,11} Current pharmacological and behavioral (ie, diet and exercise) interventions have limited long-term success in obesity.^{12–14} Thus, there is a need for more effective interventions to reduce body weight and obesity-related health disorders, both in the population at large and in people with schizophrenia in particular.

Considerable evidence from animal and human work suggests that the endocannabinoid system (acting via cannabinoid-1 [CB¹] receptors) plays an important role in obesity,^{15,16} modulating appetite drive, energy balance, and metabolic regulation.^{17–21} Cannabinoid-1 receptors are found both in the central nervous system and in the periphery in the gut, liver, skeletal muscle, pancreas, and adipose tissue.¹⁵ Rimonabant, the first CB¹ receptor antagonist approved for human use and for clinical marketing, was an effective weight loss agent in several phase 3 controlled clinical trials involving more than 12,000 participants. Its use also was associated with improvements in several metabolic parameters (ie, high-density lipoprotein, triglycerides, and adiponectin).²²

We hypothesized that rimonabant would be a promising candidate for the treatment of obesity in people with schizophrenia. We also were interested in rimonabant for schizophrenia because of evidence from animal and human studies that abnormalities in the endocannabinoid system may play a role in the etiology or expression of schizophrenia.^{23,24} This report summarizes the safety and tolerability of rimonabant in people with schizophrenia stabilized on second-generation antipsychotic medication (SGA) and rimonabant's effects on psychiatric symptoms.

MATERIALS AND METHODS

Participants

Inpatients or outpatients were enrolled if they (1) were 18 to 55 years old, (2) met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for current schizophrenia or schizoaffective disorder, (3) were treated with a SGA for at least 8 weeks and on the same dose for at least 1 month, (4) were clinically stable (as judged by treating physician), and (5) had a body mass index (BMI) of at least 30 kg/m² or at least 27 kg/m² plus hyperlipidemia or hypertriglyceridemia as defined by the adult treatment panel III guidelines.²⁵ Diagnoses were based on a best estimate diagnostic approach using information from the Structured Clinical Interview for *DSM-IV*,²⁶ clinical assessments, family informants, and medical records. Exclusion criteria included (1) significant recent depressive symptoms (suicidal ideation, suicide attempt, or hospitalization for depression in the last 6 months) or a total score of higher than 7 based on the Calgary Depression Rating

Scale (CDS)^{27,28}; (2) *DSM-IV* substance abuse (other than nicotine) within the last month or *DSM-IV* substance dependence (other than nicotine) within the last 6 months; (3) actively trying to quit cigarette smoking; (4) cannabis use greater than once weekly (to avoid cannabis withdrawal elicited by rimonabant); (5) mental retardation, dementia, traumatic brain injury, or a medical condition whose pathology or treatment could alter the presentation or treatment of schizophrenia or significantly increase the risk associated with the study; (6) history of Crohn disease, irritable bowel syndrome, eating disorders, or surgery for weight loss; (7) pregnant or breast-feeding women; and (8) taking any formulation of valproate or any medication known to alter weight or appetite (antiobesity drugs, corticosteroids, nicotine substitutes, anti-depressants, stimulants). People with type 2 diabetes mellitus were included only if their diabetes was under control, and they had been on their current diabetes medication regimen for at least 3 months. Women with childbearing potential agreed to use medically accepted means of contraception throughout the study. The study was approved by the University of Maryland Baltimore and National Institute on Drug Abuse Institutional Review Boards. Written informed consent was obtained from all participants after study procedures had been fully explained and before study participation. Participant's ability to provide valid informed consent was documented using validated study-specific procedures.²⁹

Study Design

The study had 2 phases: a 2-week lead-in phase and a 16-week, parallel group, double-blind, placebo-controlled medication phase. Participants who met eligibility criteria entered the lead-in phase to verify stability of clinical status and body weight and to allow further medical screening and collection of baseline assessments. If a participant had any change in the Clinical Global Impression (CGI) score or more than 10% change in BMI, then they were discontinued from the study. Participants who continued to meet eligibility criteria entered the double-blind medication phase and were randomized to either rimonabant, 20 mg/d or matching placebo. Participants could receive adjunctive psychotropic medications (eg, anticholinergics, beta-blockers, antidepressants, anxiolytics) if they had been prescribed for at least 6 months and at the current dose for at least 1 month before study entry.

Laboratory Assessments

A standard blood chemistry panel, complete blood count; fasting blood glucose, insulin, lipid panel, urinalysis, and electrocardiogram, were collected at baseline, midpoint, and end of study (or time of last visit). Body weight, waist circumference, and lying and standing blood pressure were measured at baseline and every 4 weeks. A urine drug screen was performed at baseline and 8 and 16 weeks. Adiponectin and HbA1C were measured at baseline and end of study. The homeostasis model of insulin resistance was calculated by multiplying fasting glucose by fasting insulin and dividing by 405.

Symptom Assessments

The Brief Psychiatric Rating Scale (BPRS) total score (18 items, each scored 1–7)³⁰ assessed general psychopathology. The BPRS 4-item positive symptom score and the BPRS anxiety/ depression factor measured changes in positive symptoms and affective symptoms, respectively. The modified Scale for the Assessment of Negative Symptoms (SANS)³¹ total score measured negative symptom change. The CGI severity of illness item measured global changes. The BPRS, SANS, and CGI were obtained biweekly. The CDS²⁷ assessed depressive symptoms weekly. Intraclass correlation coefficients for these instruments ranged from 0.76 to 0.90. All raters were blind to treatment assignment.

Weight Loss Counseling Intervention

The weight loss program was taught in 17 weekly, hour-long classes.³² The first 7 classes were individual sessions; the remaining 10 classes were group sessions with other study participants. Classes focused on a variety of topics, including healthy eating habits and the benefits of light exercise. Participants also performed a brief callisthenic exercise (eg, walking, jumping jacks, toe touches, etc) and were weighed. Participants were required to maintain a weekly diet and activity log that gauged progress outside of the sessions and as teaching tools during the weekly classes. Regular attendance in the weight loss program was strongly encouraged, but not compulsory.

Safety Assessments

The Simpson Angus Scale (SAS)³³ and the Barnes Akathisia Scale (BAS)³⁴ were administered biweekly to evaluate extra-pyramidal symptoms and akathisia, respectively. Vital signs and adverse effects were monitored by nursing staff at each visit using the Side Effect Checklist (22 common adverse effects).

Statistical Analyses

A mixed model (outcome = baseline primary outcome variable + treatment + time + time $\times$ treatment) for repeated measures analysis of variance was used to compare the changes between treatment groups of each metabolic parameter. Time was treated as a continuous variable with a scale of 0 (baseline) to 1 (end of study, 16 weeks), assuming that treatment effects for these measures would be gradual and cumulative. The slope difference provided an estimate of the difference in outcome change between rimonabant and placebo at the end of the study. A treatment $\times$ time interaction tested for treatment differences in linear trends on metabolic parameters. Baseline values were compared using the nonparametric Kruskal-Wallis test. Symptom measures that were approximately normally distributed (BPRS, SANS, and CDS) were analyzed with the mixed model analysis of covariance: follow-up score = baseline score + time + treatment + treatment $\times$ time. For symptoms, time was treated as a categorical variable to avoid assuming linear trends in symptom change. In this model, the treatment main effect estimates the average (across weeks) difference between treatments in change from baseline, which is the test for treatment effect reported here; the treatment $\times$ time factor is an exploratory test for any significant variation in the magnitude of these differences over time. This analysis method was prompted by the observation that psychiatric symptom response in clinical trials often develops and reaches a plateau relatively early,³⁵ compared with the 16-week duration of this study. All available observations from participants completing any follow-up visits were included in the mixed models for weight, metabolic factors, and psychiatric symptoms. Measures that were not normally distributed (CGI, SAS, BAS) were analyzed by computing the correlation between study week and scores within each participant, and using the Conover-Salsburg rank test to compare the distribution of the within participant correlations between groups. Adverse effects were analyzed dichotomously (yes/no) using Fisher exact test. All statistical analyses were conducted using SAS version 9 (SAS Institute Inc, Cary, NC). All tests were 2-sided with $\alpha = 0.05$.

Preplanned statistical power analyses assumed the original target study enrollment of 60 completing participants. The study was terminated prematurely after only 15 participants received medication. Rimobabant marketing was suspended in the European Union in November 2008 after the European Medicines Agency ruled that the risk/benefit ratio of rimobabant in clinical practice was no longer favorable due to psychiatric adverse effects.³⁶ Subsequently, the drug's manufacturer, Sanofiaventis, suspended all clinical development, after which both Institutional Review Boards suspended our clinical trial (February 2009).

Therefore, this study is underpowered for its primary objectives and can only be considered exploratory.

RESULTS

Study Participants

Eighteen participants enrolled in the study. One participant was withdrawn before randomization due to study termination; 17 participants underwent randomization. Two randomized participants never received study medication, 1 due to early termination and the other because of depression ratings exceeding the eligibility cutoff. Fifteen participants received double-blind study medication (7 rimonabant, 8 placebo). Five participants in each group completed the 16-week trial. Because of early study termination, 2 participants on rimonabant (at weeks 11 and 13) and 3 on placebo (at weeks 13, 13, and 15) were withdrawn before completion. No participant discontinued because of adverse events. There were no significant differences in age, sex, race, age at illness onset, or baseline psychopathology between the rimonabant and placebo groups (Table 1). The placebo group had a significantly greater baseline body weight, BMI, and waist circumference (Table 2). Antipsychotic treatment was similar in both groups. Five of 7 rimonabant participants and 4 of 8 placebo participants were outpatients.

Changes in Psychiatric Symptoms

Baseline CDS total scores were low and similar in both groups (Table 1), as expected from the eligibility criteria, and did not change significantly over the treatment period (Table 2). One placebo and 1 rimonabant participant had increases on the CDS suicidality item from 0 (absent) to 1 (mild). Rimonabant participants had a greater decrease in BPRS total score placebo participants (treatment difference: -1.9 ± 0.8 ; $t = 2.5$, $df = 30.7$, $P = 0.02$). Among the BPRS factors, the only group differences were observed in anxiety/depression and hostility; in each case the difference was due to improvement in the rimonabant group and worsening in the placebo group (Table 2). Exploratory analysis of individual items in the BPRS anxiety/depression factor suggested that most of the group difference was accounted for by reduced anxiety in the rimonabant group relative to the placebo group (mean difference [$\pm$ SE] = -1.2 ± 0.8 , $P = 0.14$) rather than to any difference in depression. There were no significant differences in the SANS total score, subscales, or CGI, although there was a trend for worsening of the anhedonia scale in the rimonabant group.

Changes in Weight and Metabolic Parameters

Six (86%) of 7 rimonabant participants and all placebo participants participated in the weekly exercise and counseling sessions. All 10 study completers attended all 17 sessions. The placebo group had significantly greater baseline BMI and waist circumference than the rimonabant group (Table 1). There were no significant group differences in change in BMI (rimonabant: $+0.3 \text{ kg/m}^2$, placebo: -0.6 kg/m^2 ; $t = 0.58$, $df = 11.2$, $P = 0.58$), or waist circumference (rimonabant: -2.4 cm , placebo: $+7.1$; $t = 0.52$, $df = 12.4$, $P = 0.61$), nor any significant group by time interactions. There were no significant treatment group differences in baseline or changes in blood pressure, pulse, or fasting laboratories (cholesterol, triglycerides, glucose, glycosylated hemoglobin, adiponectin, insulin, or homeostasis model of insulin resistance).

Adverse Effects

There were no group differences in adverse effects. The most common adverse effects were headache (3 rimonabant, 5 placebo), enuresis (4, 3), anorexia (3, 3), sedation (2, 4), abdominal pain (3, 4), weight loss (2, 4), malaise (2, 3), tinnitus (3, 2), nausea (2, 2),

dizziness (2, 2), dry mouth (2, 3), insomnia (1, 3), and vomiting (1, 1). All were not serious and usually resolved without treatment. No new onset or worsening of extra-pyramidal adverse effects or akathisia was noted. The Simpson Angus Scale and BAS total scores remained low throughout the study and did not differ significantly by group (Conover-Salsburg rank test, $F = 1.19$, $df = 1, 13$, $P = 0.30$; and $F = 0.08$, $df = 1, 13$, $P = 0.78$, respectively).

DISCUSSION

To our knowledge, this is the first study of rimonabant in people with schizophrenia for weight loss in schizophrenia. We found that rimonabant was safe and well tolerated, with no significant increases in psychiatric symptoms, including depression. To the contrary, there was significant improvement in BPRS total score and anxiety/depression and hostility factors in the rimonabant group compared with the placebo group. The decrease in anxiety/depression factor appeared primarily driven by the anxiety rather than depression items. An earlier pilot study of rimonabant (in normal weight participants) also found no significant increases in psychiatric symptoms, including no change in CDS total score.³⁷ Our findings contrast with the clinical reports of depression and suicidality in obese people prescribed rimonabant in the community that prompted the European Medicines Agency to suspend its marketing authorization.^{36,38,39} This suggests either that people with schizophrenia may be less vulnerable than others to the depression-inducing effects of rimonabant or, more likely, that careful screening of participants and close monitoring of mood during rimonabant exposure substantially reduces risk for developing depression. Published reports suggest that rimonabant-associated depressive and anxiogenic episodes are more likely and more pronounced in people with a history of depression.⁴⁰ We did note a trend towards increased anhedonia (SANS anhedonia subscale) in the rimonabant group relative to placebo (Table 2). It is possible that some depressive symptoms observed with rimonabant actually reflect anhedonia related to a disturbance of endocannabinoid modulation of brain dopaminergic reward pathways.^{41,42}

Reasons for reduced anxiety in our study are not clear. Animal and limited human data suggest a biphasic relationship between exogenous or endogenous activation of CB₁ receptors and anxiety, with differing doses being anxiolytic or anxiogenic. People with schizophrenia may have a higher anxiolytic to anxiogenic ratio of endocannabinoid function due to high tonic levels of endocannabinoids or high levels of CB₁ activation.^{43–45} Future studies that assess depression and anhedonia as distinct symptoms are needed to address this issue, as well as better understanding of rimonabant dosing in relation to psychiatric symptoms.

A major limitation of this study is the small sample size, due to its premature termination, and consequent limited power to detect efficacy or rare adverse events. This may explain the failure to observe the beneficial effects on BMI and metabolic parameters that were hypothesized based on published trials in overweight or obese subjects without schizophrenia. Nonetheless, rimonabant was well tolerated in this group, was not associated with worsening of psychiatric symptoms, including depressive symptoms, and in some cases was associated with symptom reduction. Our results suggest that the endocannabinoid system remains a promising target for pharmacotherapy of schizophrenia and obesity.^{46,47}

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TABLE 1

Demographic and Baseline Clinical Characteristics

	Rimonabant (n = 7)	Placebo (n = 8)	Significance
Age, y	45.9 ± 6.9	42.4 ± 13.3	$\chi^2 = 0.12$, $df = 1$, $P = 0.73$
Sex, male	5 (71%)	4 (50%)	$P = 0.61^*$
Race, white	4 (57%)	3 (38%)	$P = 0.62^*$
Age of illness onset, y	22.4 ± 11.1	22.5 ± 7.3	$\chi^2 = 0.13$, $df = 1$, $P = 0.72$
BPRS total score	33.5 ± 7.5	34.5 ± 4.6	$\chi^2 = 0.05$, $df = 1$, $P = 0.82$
SANS total score	28.7 ± 10.9	26.7 ± 15.5	$\chi^2 = 0.66$, $df = 1$, $P = 0.42$
CDS total score	3.0 ± 2.2	3.0 ± 2.4	$\chi^2 = 0.00$, $df = 1$, $P = 0.95$
BMI, kg/m ² *	31.3 ± 3.2	43.8 ± 13.2	$\chi^2 = 4.3$, $df = 1$, $P = 0.04$
Antipsychotic or combination			
Clozapine	3 (43%)	1 (13%)	$P = 0.28^*$
Clozapine + SGA	0 (0%)	2 (25%)	$P = 0.47^*$
Olanzapine + SGA	1 (14%)	0 (0%)	$P = 0.47^*$
Risperidone ± SGA (not clozapine or olanzapine)	3 (43%)	2 (25%)	$P = 0.61^*$
Quetiapine ± SGA (not clozapine or olanzapine)	0 (0%)	1 (13%)	$P = 1.0^*$
Ziprasidone	0 (0%)	2 (25%)	$P = 0.47^*$
Adjunctive medications			
Antidepressants	3 (43%)	3 (38%)	$P = 1.0^*$
Cholesterol lowering medication	3 (50%)	3 (38%)	$P = 1.0^*$
Antidiabetic medication	0 (0%)	1 (13%)	$P = 1.0^*$
Antihypertensive medication	2 (33%)	2 (25%)	$P = 1.0^*$

* Fisher exact test.

TABLE 2

Changes in Psychopathology During the 16-Week Trial

	Rimonabant (n = 7 BL, n = 5 EOS)		Placebo (n = 8 BL, N = 5 EOS)		Mixed Model Treatment Difference Estimates
	Weeks	Assessment	Weeks	Assessment	
BPRS total score	0	33.5 ± 7.5	0	34.5 ± 4.6	-1.9 ± 0.8, <i>t</i> = 2.5, <i>df</i> = 30.7, <i>P</i> = 0.02
	16	32.8 ± 3.9	16	33.6 ± 6.2	
BPRS positive symptom items	0	9.4 ± 4.3	0	11.4 ± 3.4	-0.4 ± 0.4, <i>t</i> = 1.2, <i>df</i> = 27.9, <i>P</i> = 0.25
	16	7.6 ± 3.0	16	8.6 ± 3.4	
BPRS anxiety/depression factor	0	6.1 ± 2.5	0	5.4 ± 1.2	-1.4 ± 0.4, <i>t</i> = 4.0, <i>df</i> = 29.5, <i>P</i> = 0.0004
	16	5.2 ± 1.6	16	6.4 ± 2.3	
BPRS hostility factor	0	4.9 ± 1.2	0	4.8 ± 0.9	-0.7 ± 0.3, <i>t</i> = 2.5, <i>df</i> = 26.9, <i>P</i> = 0.02
	16	4.2 ± 1.3	16	5.0 ± 2.0	
BPRS activation factor	0	4.1 ± 0.6	0	3.6 ± 0.8	-0.5 ± 0.3, <i>t</i> = 1.8, <i>df</i> = 25.1, <i>P</i> = 0.09
	16	3.6 ± 0.9	16	5.0 ± 1.9	
SANS total score	0	28.7 ± 10.9	0	26.7 ± 15.5	2.0 ± 1.3, <i>t</i> = -1.5, <i>df</i> = 23.7, <i>P</i> = 0.13
	16	33.2 ± 11.6	16	32.4 ± 15.8	
SANS anhedonia *	0	1.9 ± 1.0	0	1.6 ± 0.9	0.3 ± 0.2, <i>t</i> = -1.8, <i>df</i> = 21.2, <i>P</i> = 0.09
	16	1.9 ± 1.0	16	1.9 ± 1.1	
SANS blunted affect	0	1.3 ± 0.9	0	1.1 ± 1.0	0.2 ± 0.1, <i>t</i> = -1.3, <i>df</i> = 24.2, <i>P</i> = 0.20
	16	1.8 ± 0.9	16	1.2 ± 1.0	
SANS alogia	0	0.5 ± 0.5	0	0.9 ± 1.4	0.04 ± 0.1, <i>t</i> = -0.3, <i>df</i> = 18.7, <i>P</i> = 0.75
	16	0.9 ± 1.1	16	1.4 ± 1.3	
SANS avolition	0	2.6 ± 1.1	0	2.4 ± 1.1	-0.1 ± 0.2, <i>t</i> = 0.4, <i>df</i> = 20.7, <i>P</i> = 0.67
	16	2.6 ± 1.2	16	3.0 ± 1.2	
CGI	0	4.2 ± 0.4	0	4.2 ± 0.7	-0.01 ± 0.1, <i>t</i> = 0.2, <i>df</i> = 26.1, <i>P</i> = 0.88
	16	4.2 ± 0.4	16	4.0 ± 1.0	
CDS total score	0	3.0 ± 2.2	0	3.0 ± 2.4	0.3 ± 0.3, <i>t</i> = -1.18, <i>df</i> = 42.75, <i>P</i> = 0.24
	16	2.0 ± 2.5	16	2.0 ± 2.7	

Ratings were performed every 2 weeks. Mixed models were used to estimate the average magnitude of treatment difference for all follow-up visits.

*Trend for increase in anhedonia during the study—For rimonabant: BL 1.9 ± 1.0 week 2 (n = 7); 1.8 ± 1.2 ; week 4 (n = 7); 2.1 ± 1.1 ; week 6 (n = 7) 2.3 ± 1.0 ; week 8 (n = 7); 1.9 ± 1.3 ; week 10 (n = 7); 2.2 ± 0.9 ; week 12 (n = 6); 2.0 ± 0.8 ; week 14 (n = 5); 1.9 ± 1.0 . For placebo: BL (n = 8); 1.6 ± 0.9 ; week 2 (n = 8); 1.4 ± 0.8 ; week 4 (n = 8); 1.4 ± 1.2 ; week 6 (n = 8) 1.5 ± 1.0 ; week 8 (n = 8); 1.5 ± 1.0 ; week 10 (n = 8); 1.8 ± 1.2 ; week 12 (n = 8); 1.5 ± 0.9 ; week 14 (n = 6); 1.3 ± 1.4 ; EOS (n = 5); 1.9 ± 1.1 . BL indicates baseline; EOS, end of study.