A Multicenter, Placebo-Controlled, Double-Blind, Randomized Study of Efficacy and Safety of Ocinalon (DOV 273,547) in Generalized Anxiety Disorder

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*Deceased. This paper is dedicated to his memory.

Preclinical studies demonstrated that ocinalon, a positive allosteric modulator of GABA_A receptors, possesses anxiolytic-like actions at doses devoid of the side effects typically associated with benzodiazepines. The aim of this study was to evaluate the effects of ocinalon in a multicenter, double-blind proof-of-concept trial of male and female outpatients who met DSM-IV criteria for GAD with no coexisting depression, and had a baseline score of ≥ 20 on the Hamilton Scale for Anxiety (HAM-A). Patients with $< 20\%$ reduction in HAM-A to placebo in a single-blind 7-day run-in period were randomly assigned to treatment with ocinalon 90 mg t.i.d. ($n = 31$) or placebo for 28 days ($n = 29$). Ocinalon was more effective than placebo in reducing HAM-A scores ($P = 0.009$). Patients assigned to ocinalon exhibited a mean improvement of 14.2 points (SE = 2.6) on the total score of the HAM-A scale at the conclusion of the trial, while patients assigned to placebo obtained a mean improvement of 6.3 points (SE = 2.0). A significant ($P = 0.023$) difference in improvement between ocinalon and placebo was observed beginning at and continuing from 1-week after the initiation of dosing. The proportion of patients with treatment-emergent adverse events (TEAE) was not statistically significant between ocinalon and placebo. One serious adverse event (SAE) occurred in the ocinalon group that was considered possibly related to study medication (icterus following transaminase elevations). The patient had preexisting medical conditions that may have contributed to this SAE. A full recovery was observed with no residual effects. The overall safety profile revealed no patterns of TEAEs, including those effects typically associated with other anxiolytic and/or benzodiazepine compounds, such as sedation. Ocinalon appears to be a well-tolerated and effective treatment for GAD. It produces a rapid onset of anxiolytic action absent the side effects (e.g., dizziness, sedation) typically reported following anxiolytic doses of benzodiazepines.

Introduction

According to a multicenter study by the World Health Organization [1], generalized anxiety disorder (GAD) is the second most commonly diagnosed psychiatric disorder in primary care settings, with a lifetime prevalence of 5.1%

in the United States [2]. It has a devastating impact on quality of life, and places a significant financial burden on society [3,4]. Current pharmacological treatment options for GAD are not fully satisfactory.

Among the available pharmacological treatments for GAD, benzodiazepines (BZ) have a long history of

clinical use. These medications are thought to elicit a wide spectrum of behavioral and clinical changes via enhancing the actions of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) subsequent to binding at specific recognition sites on GABA_A receptors [5–7]. Benzodiazepines characteristically produce a rapid onset of therapeutic action, and play an important role in treating severe and acute situations in which an immediate anxiolysis is required [8,9]. However, benzodiazepines are no longer considered first line therapy for the treatment of GAD despite a continued, widespread use [9,10]. There are multiple reasons for the decline in popularity of BZs, but none related to the introduction of more effective agents in the treatment of GAD. Undesirable side effects (e.g., amnesia, sedation, and ataxia), concerns about abuse potential and a withdrawal syndrome, controversy about long-term efficacy including relapse and recurrence [11], and the lack of incentive to promote generic drugs have all contributed to a reduction in the use of these compounds.

Among antidepressants that are currently approved by the FDA for GAD, selective serotonin reuptake inhibitors (SSRIs) such as escitalopram and paroxetine, are generally considered to be the first-line therapy for GAD [8,9]. These compounds are relatively safe and do not appear to produce dependence. However, SSRIs have a delayed onset of action and produce only modest clinical effects that constrain their benefit in practice. For example, a large clinical trial of escitalopram showed a statistically significant separation from placebo after 1-week treatment but *clinically*, the effects of the test drug were almost indistinguishable from those of placebo at this time point (<2 points on the HAM-A scale) [12]. In another large study, the SSRI antidepressant paroxetine and placebo produced essentially identical effects after 1 week of treatment and a statistically significant separation between active and placebo emerged only after 6 weeks (<2 points on HAM-A scale) [13].

Although the azapirone buspirone does not possess either the dependence risk or side effect profile of BZs, it is generally viewed as less efficacious, and provides a slow onset of action with relatively poor long-term efficacy [9,14]. Venlafaxine, the selective serotonin and norepinephrine reuptake inhibitor (SNRI) that was approved for the treatment of GAD, offers maintained therapeutic effects over long treatment periods but with a lower overall efficacy than BZs. Moreover, venlafaxine has not consistently produced therapeutic effects within 1 week of treatment [15–17] as has been shown for BZs. In addition, an increase of blood pressure associated with such treatment may become clinically significant and requires long-term monitoring, especially in patients that require higher doses [18].

In view of the limitations of current therapies, one avenue of pharmacological research has focused on developing novel “anxioselectives,” drugs capable of producing a rapid and robust anxiolysis associated with BZs, but with a reduced potential for sedation and related side effects [5,6,19–24]. A number of compounds have been identified that act through the GABA_A receptors targeted by BZs, and exhibit subtype selectivity and/or lower efficacy than “classical” 1,4-benzodiazepines (e.g., diazepam) to augment GABA stimulated chloride currents [5,6]. Although a subset of these compounds exhibited an anxioselective profile in animals, clinical studies have not demonstrated the anxioreselectivity predicted from their preclinical profiles [22,23,25].

Ocinaplon (DOV 273,547), a positive allosteric modulator at GABA_A receptors, produces robust anxiolytic-like effects in preclinical models at doses that are devoid of the side effects of “classical” BZs [24]. In particular, both the ability to increase punished responding in conflict procedures, and to antagonize clonic convulsions produced by pentylenetetrazole (PTZ), are considered highly predictive of the ability of a drug to produce anxiolytic effects in humans [21,26,27] when tested in standardized rat and monkey conflict procedures, ocinaplon produced dose-related increases in punished responding with an efficacy and potency comparable to the prototypic BZ, diazepam [24]. Ocina-plon and diazepam also decreased PTZ-induced convulsions in rats with similar potencies. These effects were observed at doses that were considerably lower than those producing motor depression, ataxia, and muscle relaxation in the rat and a reduction in operant responding in the monkey [24]. The anticonflict actions of ocinaplon are blocked by flumazenil (Ro 15–1788), *prima facie* evidence that, like BZs, the pharmacological effects of ocinaplon are produced at GABA_A receptors [6]. Ocina-plon exhibits a low affinity, partial agonist profile at recombinant GABA_A receptors [24]. However, it is unknown if this molecular profile is either necessary or sufficient to produce an anxioreselective profile [5,7,20].

Based on these preclinical data demonstrating a potential anxioreselective profile, it was decided to investigate whether ocinaplon might provide a therapeutic alternative to agents currently used for the treatment of GAD. In a short, 2-week study in patients with GAD, ocinaplon significantly reduced HAM-A scores in the absence of any side effects typically associated with BZs [24,28]. The absence of BZ-like side effects was also observed in single and multiple dose Phase I studies in normal volunteers. The present study investigated the effects of ocinaplon in GAD patients after 4-week administration, a longer trial duration that is more comparable to what has been reported in clinical trials with other anxiolytics.

Patients and Methods

Study Design

This was a multicenter, prospective, double-blind, randomized placebo-controlled trial in which outpatients with the diagnosis of GAD were assigned to one of two treatment groups: ocinaplon (90 mg, t.i.d.) or placebo. The study had an initial, single-blind 7-day screening/placebo run-in period during which patient eligibility was determined. Inclusion and exclusion criteria included an assessment of clinical response to placebo (<20% improvement on the Hamilton Anxiety [HAM-A] Scale [29]) as well as compliance with the prescribed dosing schedule (pill count compliance between 75% and 115%). Eligible patients were enrolled in the 28-day double-blind treatment period; active study medication was administered at a fixed daily dose (270 mg; 90 mg t.i.d.). The double-blind treatment phase was followed by a 7-day posttreatment follow-up period during which patients were tapered off the study drug. During this poststudy tapering period, the dosing was scheduled according to an initial twice-daily regimen (90 mg b.i.d. + 1 placebo) for the first 3 days, followed by a once-daily regimen (90 mg QD + 2 placebos) for the subsequent 3 days, and no medications or placebo on poststudy day 7 and thereafter. The study was approved by the appropriate Ethics Committee and Institutional Review Boards. All participants gave written informed consent to the procedures after a thorough explanation of the objectives, risks, and benefits of the study had been given to them.

Patient Group

Subjects were 18–60-year old outpatients with the DSM-IV diagnosis of GAD [30] enrolled in eight participating centers in Germany. For inclusion, the subjects had to evidence sufficient initial symptom severity to require treatment (≥ 20 on the total score of the HAM-A scale) and no coexisting depressive symptoms (total score on the Hamilton Rating Scale for Depression [31] [HAM-D] ≤ 15). In addition, patients were required to have normal vital signs, with no clinically significant changes in laboratory assessments, including clinical chemistry, hematology, and urinalysis. Negative test results for hepatitis B screen, serum pregnancy test, and urine drug screen (amphetamines, antidepressants, alcohol, barbiturates, benzodiazepines, buspirone, cocaine, hallucinogens, opiates, and tetrahydrocannabinol) were also required.

Patients were excluded if they had a recent (<12 months) DSM-IV diagnosis of major depressive episode; schizophrenia or any psychotic disorder; primary diagnosis of panic disorder; history of seizure

disorder, organic brain disease, severe allergies, multiple adverse drug reactions, and any adverse or untoward reaction to benzodiazepines or barbiturates; or a recent (<12 months) history of alcohol or drug abuse (excluding nicotine) that may suggest drug or alcohol use risk during the study. Patients were also excluded if the MINI International Neuropsychiatric Interview (M.I.N.I.) indicated current major depressive episode, suicidality, (hypo)manic episode, panic disorder, obsessive compulsive disorder, drug or alcohol dependence/abuse, psychotic disorders, and anorexia nervosa. In addition, patients were not allowed to receive any of the following types of medication within 7 days prior to the screening/placebo run-in period: sedating antihistamines, psychotropics, anticonvulsants, centrally acting beta-blockers, clonidine, H_2 antagonists other than ranitidine, theophylline, and thyroid hormones.

Assessments

Efficacy

The Hamilton Anxiety Rating Scale was the principal measure of efficacy. It was administered at the beginning and at the end of the screening/placebo run-in period and then at every week thereafter. Secondary measures of efficacy included the Clinical Global Impression Scale (CGI) [32], the patient's self-rating scale (SRS) for generalized anxiety, and the patient's global evaluation. Analogous to the principal measure of efficacy, secondary measures were obtained at every week (visit) during the study.

Safety

Adverse events were evaluated at baseline (end of screening/placebo run-in period) and subsequently every week. Information concerning adverse events was obtained from spontaneous patient reports and investigator inquiry. Vital signs and use of concomitant medications were monitored at each assessment. Physical examinations, clinical chemistry, urinalysis, and hematology assessments were performed at the beginning and at the end of each period in the study (i.e., screening/placebo, double-blind treatment, posttreatment). Each nonlaboratory adverse experience reported by the patients was rated for its severity (1 = "mild," 2 = "moderate," 3 = "severe," 4 = "life threatening") and for its relationship with the study drug (1 = "definitely," 2 = "probably," 3 = "possibly," 4 = "remotely," 5 = "definitely not").

Eligibility

The following evaluations were performed at the beginning of the screening period in order to determine

basic patient eligibility: Medical History, MINI Interview, Hamilton Depression Scale, Urine Drug, and Hepatitis B Screen. A plasma screen for benzodiazepines was also performed at the beginning and at end of the double-blind period.

Concomitant Medications

The following concomitant medications were not permitted at any time during the course of the study: sedating antihistamines, psychotropics, anticonvulsants, opiates, benzodiazepines, centrally acting beta-blockers, clonidine, H₂ antagonists other than ranitidine, theophylline, thyroid medications, muscle relaxants, and alcohol. Chloral hydrate was permitted for insomnia but not within 24 h prior to any clinic visit.

Statistical Analyses

The principal statistical analysis of efficacy tested the hypothesis that the global antianxiety effects of ocinaplon are superior to placebo. The total score on the Hamilton Anxiety Scale (HAM-A total) was adopted as the primary measure of efficacy.

Two basic approaches were adopted to analyze all available data from the entire sample (i.e., cases with complete and incomplete data): (1) the random regression hierarchical linear modeling (HLM) [33–35], which permits the use of observations with incomplete data (e.g., patients who drop out before completing the study); and (2) the traditional analysis of covariance (ANCOVA) analysis of change over time (endpoint, or last observation carried forward analysis for *observed change* at study endpoint for each subject), with baseline severity as a covariate. Since the HLM (in contrast to the traditional ANCOVA approach) makes allowance for censored observations and for heterogeneity among treatment groups both in terms of baseline values and in terms of covariance structure (i.e., relationship between baseline severity and change), the HLM analysis was chosen as the primary statistical approach for the study.

In the HLM model, repeated assessments of symptom severity over time (i.e., HAM-A total) served as the dependent variable. The two independent variables were the “treatment group” and “time.” Treatment group served as the between subject factor. Time (in weeks) elapsed from the baseline was used as the within subject, random effect factor. Center (study site) was applied in the model as a random effect. Interaction between treatment group and time was included in the model. An unstructured covariance matrix allowing for heterogeneity among treatment groups was specified in the HLM model. The time effect and the interaction ef-

fect were tested by the *F*-statistic. If a significant effect was detected, posthoc analyses were performed to examine the direction of changes (time effect) or the differences in change over time among the treatment groups (interaction effect).

Additional HLM analyses, analogous to that described for the principal measure (i.e., total score on the HAM-A scale) were performed for the secondary measures. Secondary measures of efficacy included the score on the Psychic and Somatic Factors on the HAM-A scale [29]; the total score on the SRS; the Patient’s Global Evaluation; and the CGI (severity and improvement). A non-parametric survival analysis with Kaplan–Meier estimates tested whether the two treatment groups differed in terms of time-to-attrition (“survival”) in the study. Categorical variables (e.g., frequency of adverse events) in the two treatment groups were investigated by χ^2 analysis and Fisher’s exact test (for events with low frequency). An α -level of 0.05 (one-sided) was adopted for all analyses of statistical significance of efficacy. While the one-sided test was prespecified in the protocol, we note that in the current publication we indicate whenever a result did not reach statistical significance with the more robust two-sided approach.

Results

Patient Attrition and Demographics

A total of 60 subjects were assigned to treatment and qualified for the intent-to-treat analyses (ocinaplon = 31, placebo = 29). Out of the 60 subjects, 5 subjects (ocinaplon = 3; placebo = 2) discontinued the study before the end of the first treatment week with no evaluable measurement for efficacy. Three of these early withdrawals were due to administrative reasons (termination of the trial by the sponsor; ocinaplon = 1, placebo = 2). In addition, 1 patient in the ocinaplon group was discontinued from the trial for taking a concomitant medication (synthetic thyroid hormone) not permitted by the protocol. One patient (ocinaplon group) was discontinued from the study for testing positive for a drug of abuse. Thus, the set of patients with basic efficacy data included 55 subjects, 28 and 27 in the ocinaplon and the placebo group, respectively.

The entire 4 weeks of the study was completed by 23 subjects (ocinaplon = 13; placebo = 10). The difference in the overall rate of completion between the two treatment groups was not statistically significant. The reason for the relatively low completion rate was that the study was terminated by the sponsor in order to evaluate a patient with marked transaminase elevations followed by jaundice and to ensure a thorough evaluation of this

Table 1 Basic descriptive and demographic information

Characteristic ^a	Ocinaplon (N = 31)		Placebo (N = 29)	
	N	%	N	%
Gender: Male	10	32	11	38
Female	21	68	18	62
	Mean	SD	Mean	SD
Age (years)	44.9	9.5	44.7	11.3
CGI severity	5.8	1.0	5.8	1.0
HAM-A total	30.7	6.5	32.4	7.2
HAM-D total	11.6	2.3	11.7	2.2

^aNo significant group difference on any of the variables.

patient and the hepatic data from the prior studies. The case of marked transaminase elevations followed by jaundice is described below.

Thus, the distribution of patient dispositions at the end of the trial indicated that the most frequent reason for early discontinuation was the termination of the trial by the sponsor (ocinaplon = 14; placebo = 17). Consent withdrawal occurred in two subjects (ocinaplon = 1; placebo = 1). One subject (placebo group) had positive test results for use of antidepressants. The remaining reasons (occurring in the ocinaplon arm) included the use of tetrahydrocannabinol ($n = 1$); prescription of concomitant medication not permitted in the study ($n = 1$); and a serious adverse event (inguinal hernia; $n = 1$).

The demographic characteristics of all randomized subjects ($n = 60$) are displayed in Table 1. No statistically significant differences in basic demographic characteris-

tics were detected between the ocinaplon- and placebo-treated subjects.

Analyses of Efficacy

Change Over Time

The intent-to-treat analysis of the primary efficacy measure (HAM-A total) was based on the hierarchical linear model, which makes allowance for the analyses of all randomized subjects, including cases with incomplete data (e.g., early withdrawals). The HLM results showed a significant interaction between time and treatment ($F = 5.9$, $P = 0.009$), indicating that the two treatment groups differed in terms of change in symptom severity over time. The HLM estimates of change showed that, on the average, patients assigned to the ocinaplon group obtained a mean improvement of 14.2 points ($SE = 2.6$) on the total score of the HAM-A scale ($P = 0.00005$) by the end of the 4-week trial. Patients assigned to placebo obtained a mean improvement of 6.3 points ($SE = 2.0$; $P = 0.001$). The improvement, as compared to the pretreatment baseline, reached statistical significance in both groups (Table 2).

Due to the unbalanced gender distribution with nearly twice as many females as males in the study (Table 1), we conducted a separate HLM analysis by gender in order to investigate whether our principal findings in terms of a significant treatment difference in improvement were observable across genders. Results of these analyses indicated that both for females and males the active treatment showed significantly more improvement than

Table 2 Analyses of change over time during double-blind treatment^a

Variable	GROUP ^b	Estimated change over 4 weeks mean $\pm$ SE	Test of time effect (reduction in symptom severity)	Test of group difference in change
HAM-A total score	Ocinaplon	14.2 $\pm$ 2.6	$t = 5.6$, $P = 0.00005$	$F = 5.9$, $P = 0.009$
	Placebo	6.3 $\pm$ 2.0	$t = 3.2$, $P = 0.001$	
Psychic factor	Ocinaplon	6.8 $\pm$ 1.4	$t = 4.8$, $P = 0.00005$	$F = 5.6$, $P = 0.01$
	Placebo	2.5 $\pm$ 1.1	$t = 2.3$, $P = 0.01$	
Somatic factor	Ocinaplon	7.3 $\pm$ 1.2	$t = 6.2$, $P = 0.00005$	$F = 5.3$, $P = 0.01$
	Placebo	3.7 $\pm$ 1.0	$t = 3.7$, $P = 0.0005$	
Patient self-rating scale	Ocinaplon	17.8 $\pm$ 3.8	$t = 4.7$, $P = 0.00005$	$F = 7.0$, $P = 0.005$
	Placebo	6.0 $\pm$ 2.3	$t = 2.6$, $P = 0.006$	
Patient global evaluation	Ocinaplon	1.9 $\pm$ 0.4	$t = 4.6$, $P = 0.00005$	$F = 5.4$, $P = 0.01$
	Placebo	0.6 $\pm$ 0.4	$t = 1.4$ n.s.	
Clinical global impression	Ocinaplon	1.8 $\pm$ 0.4	$t = 4.3$, $P = 0.00005$	$F = 2.7$, $P = 0.049^c$
	Placebo	0.9 $\pm$ 0.4	$t = 2.3$, $P = 0.01$	

^aHierarchical linear model analysis was conducted for each measure (see text).

^bN = 31 for ocinaplon; N = 29 for placebo.

^cMarginally significant ($P < 0.1$) with the two-sided test.

Figure 1 Anxiolytic effects of ocinaplon in generalized anxiety disorder (GAD). Eligible patients (Hamilton Anxiety Scale score ≥ 20) with a diagnosis of GAD were randomized into two groups receiving either ocinaplon (90 mg three times daily) or placebo. Random regression hierarchical linear model (HLM) analysis indicated that ocinaplon produced a significantly greater reduction in symptom severity compared with placebo ($F = 5.9$; $df = 1, 53$; $P = 0.009$). Symptom change trajectories over time for patients assigned to ocinaplon ($n = 31$) and placebo ($n = 29$), respectively, were estimated on the basis of the HLM model.

placebo in change in symptom severity over time (for females interaction $F = 6.7$, $P = 0.014$, estimated mean treatment difference in improvement [SE] at the end of the 4-week trial = 6.1 [2.4] points; for males $F = 6.0$, $P = 0.026$, difference in improvement = 9.3 [3.6] points).

Symptom change trajectories over time in the two treatment groups are depicted in Figure 1. Similar to the

analyses of primary efficacy variable HAM-A total, HLM analysis was performed for each of the secondary measures, including the psychic and somatic factors on the HAM-A scale, the total score on the SRS, the Patient's Global Evaluation and the CGI. The analysis yielded a significant group by time interaction for each measure (Table 2), indicating that ocinaplon produced a significantly greater improvement than placebo (Table 2) on all secondary measures.

Endpoint Analysis

The ANCOVA analyses were based on the observed endpoint efficacy data from the subjects who were randomized and provided at least one evaluable measurement during the double-blind phase of the trial ($n = 55$; ocinaplon = 28, placebo = 27). Change in the HAM-A total in each patient at the study endpoint served as dependent variable in the ANCOVA model (i.e., endpoint analysis with the last observation carried forward [LOCF] approach). Table 3 summarizes the results of the primary efficacy variable HAM-A total and for each of the secondary measures; the two treatment groups had essentially the same initial symptom severity on all measures of efficacy ($P > 0.1$ for each of the measures).

Similar to the HLM, the ANCOVA results indicated significant superiority of ocinaplon versus placebo ($F = 7.5$; $df = 1, 54$; $P = 0.004$). The mean overall reduction of symptom severity was 10.5 (SD = 10.5) and 4.5 (SD = 7.1) for the ocinaplon and the placebo group,

Table 3 Endpoint analyses^a for the double-blind period

Variable	Group	Baseline mean ^c $\pm$ SD	Endpoint ^b mean ^d $\pm$ SD	Change at endpoint mean ^d $\pm$ SD	Test of time effect at endpoint	Test of group difference in change
HAM-A total score	Ocinaplon	30.9 $\pm$ 7.1	20.5 $\pm$ 8.4	10.5 $\pm$ 10.5	$t = 5.3$, $P = 0.00005$	$F = 7.5$, $P = 0.004$
	Placebo	32.9 $\pm$ 7.2	28.2 $\pm$ 11.1	4.5 $\pm$ 7.1	$t = 3.3$, $P = 0.001$	
Psychic factor	Ocinaplon	15.8 $\pm$ 4.2	10.6 $\pm$ 4.9	5.0 $\pm$ 6.0	$t = 4.4$, $P = 0.0001$	$F = 7.2$, $P = 0.005$
	Placebo	17.2 $\pm$ 3.9	15.2 $\pm$ 6.0	1.9 $\pm$ 3.9	$t = 2.5$, $P = 0.009$	
Somatic factor	Ocinaplon	15.1 $\pm$ 4.2	9.9 $\pm$ 4.2	5.5 $\pm$ 4.9	$t = 5.9$, $P = 0.00005$	$F = 6.9$, $P = 0.006$
	Placebo	15.7 $\pm$ 4.2	13.0 $\pm$ 5.6	2.6 $\pm$ 3.6	$t = 3.7$, $P = 0.0005$	
Patient self-rating scale	Ocinaplon	42.5 $\pm$ 11.6	28.1 $\pm$ 14.4	13.5 $\pm$ 16.0	$t = 4.5$, $P = 0.00005$	$F = 7.6$, $P = 0.004$
	Placebo	42.0 $\pm$ 13.1	37.7 $\pm$ 17.0	4.3 $\pm$ 7.6	$t = 2.9$, $P = 0.003$	
Patient global evaluation	Ocinaplon	4.1 $\pm$ 0.9	2.6 $\pm$ 1.3	1.5 $\pm$ 1.6	$t = 4.8$, $P = 0.00005$	$F = 9.7$, $P = 0.002$
	Placebo	4.2 $\pm$ 0.9	3.7 $\pm$ 1.3	0.5 $\pm$ 1.4	$t = 1.9$, $P = 0.03^e$	
Clinical global impression	Ocinaplon	5.7 $\pm$ 0.9	4.4 $\pm$ 2.0	1.4 $\pm$ 1.5	$t = 4.9$, $P = 0.00005$	$F = 3.3$, $P = 0.04^e$
	Placebo	6.0 $\pm$ 1.1	5.4 $\pm$ 1.5	0.6 $\pm$ 1.5	$t = 2.2$, $P = 0.02$	

^aAnalysis of covariance was conducted for each measure with baseline severity as a covariate (see text).

^bEndpoint is based on the last observation carried forward (LOCF) approach.

^c $N = 31$ for ocinaplon; $N = 29$ for placebo.

^d $N = 28$ for ocinaplon; $N = 27$ for placebo.

^eMarginally significant ($P < 0.1$) with the two-sided test.

respectively (Table 3). The statistical effect size for change over time was approximately 1.0 for the test drug; standardized effects of similar magnitude (i.e., 0.8 or greater) are generally considered large [36]. In addition, the ANCOVA analyses yielded significant difference between the two treatment groups for each of the secondary measures ($P < 0.05$ for all secondary variables). In particular, both placebo and ocinaplon produced a statistically significant symptom reduction at the endpoint of the study, but patients treated with ocinaplon displayed a substantially greater improvement than patients treated with placebo (Table 3).

Early Therapeutic Effects and Analyses by Week

ANCOVA was performed to investigate whether a statistically significant difference in the principal measure of efficacy between the active and placebo group was present after 1 week of treatment (i.e., at the first efficacy measurement in the double-blind phase). Results showed a significant superiority for ocinaplon over placebo in the reduction of symptom severity at the 1-week assessment, with mean improvements on HAM-A total of 5.3 (SD = 7.5) and 2.8 (SD = 3.5) in the ocinaplon and the placebo groups, respectively ($F = 4.2$; $df = 1, 54$; $P = 0.023$).

Analyses of the mean improvements in HAM-A total by week indicated that the significant difference between the two treatments was maintained at week 2 (mean improvement: ocinaplon = 9.5 [SD = 9.2], placebo = 4.4 [4.8]; $F = 6.3$; $df = 1, 46$; $P = 0.008$) and week 3 (mean improvement: ocinaplon = 11.8 [SD = 10.0], placebo = 4.4 [6.7]; $F = 4.9$; $df = 1, 30$; $P = 0.018$). Due to the small sample size, the difference did not reach statistical significance at week 4, although the treatment effect remained essentially unchanged from week 3 (mean improvement: ocinaplon = 11.7 [SD = 10.2], placebo = 5.0 [9.2]; $F = 2.4$; $df = 1, 22$; $P = 0.068$).

Time to Onset of Clinical Response

Clinical response was defined by the improvement on the clinical global impression scale [13,37]. The criterion for clinical response was fulfilled if a rating of "much improved" or "very much improved" was obtained on the CGI scale. Survival analysis indicated a significant difference between the two study groups in terms of time-to-response (log-rank test, $\chi^2 = 5.6$; $P = 0.01$). The mean onset time to achieve clinical response was approximately 2.2 weeks (SE = 0.15) and 3.4 weeks (SE = 0.23) in the ocinaplon and the placebo group, respectively. By the end of the double-blind phase of the trial, the estimated rate of clinical response was 74% and 35%, for the ocinaplon and the placebo group, respectively.

Completers' Analysis

The analyses focused on the principal efficacy measure (HAM-A total), and examined whether results similar to those in the full sample were manifested in patients who completed at least 3 of 4 weeks of the double-blind phase of the trial. The HLM analysis yielded a significant time by treatment group interaction ($F = 4.1$; $df = 1, 29$; $P = 0.03$), indicating a difference in symptom reduction between the two groups. The estimated mean reduction of symptom severity (HAM-A total) was 12.9 (SE = 2.6; $n = 17$) and 5.4 (SE = 2.7, $n = 14$) in the ocinaplon and the placebo group, respectively. The ANCOVA analysis of the LOCF endpoints also showed a significantly greater improvement for ocinaplon as compared to placebo ($F = 3.7$, $df = 1, 30$, $P = 0.03$). The observed improvement at study endpoint in the completers' sample was 12.4 ± 10.8 and 4.8 ± 9.2 in the ocinaplon and placebo group, respectively. (We note that the above two tests of interaction were marginally significant under the more stringent two-sided approach, i.e., $P = 0.06$ for the HLM and ANCOVA, respectively.)

Follow-Up Analysis

Patients were followed-up for an additional week after completion of the double-blind phase. During this post-treatment period, study medication was gradually tapered and final evaluations were performed at the end of this period. Change during this period was defined by the difference in symptom severity on the HAM-A total between the endpoint of the double-blind and the follow-up period (a negative sign signifies an increase in severity). The analysis was conducted for the full sample and then repeated for the sample of patients who completed the entire 28-day treatment period, since it was expected that any potential withdrawal and rebound effects would be more pronounced in the latter sample. The results of the two ANCOVA analyses yielded no significant group effect ($P > 0.8$ in both analyses). Overall, for both groups, the change over time with group was neither statistically significant (paired *t*-test for each group) nor clinically meaningful. In the full sample, the change was -0.4 points (SD = 7.5, $n = 28$) and 0.6 point (SD = 3.1, $n = 27$) in the active and placebo group, respectively. Results were similar in the completers' sample (change in HAM-A total = -1.4 points [SD = 9.8, $n = 13$] and -1.2 point [SD = 3.2, $n = 10$] in the active and placebo group, respectively).

Safety Analyses

Treatment-emergent adverse events (TEAE) occurred in 12 (20%) of the 60 subjects who received at least

Table 4 Treatment-emergent adverse events (AEs), ocinaplon versus placebo

MedDRA system organ		Number (%) of patients	
		Ocinaplon (N = 31)	Placebo (N = 29)
Classification	MedDRA preferred term		
One or more AEs	All Subjects with AEs	9 (29.0)	3 (10.3)
Gastrointestinal disorders	Subjects with AEs	3 (9.7)	1 (3.4)
	Abdominal pain NOS	0 (0.0)	1 (3.4)
	Diarrhoea NOS	0 (0.0)	1 (3.4)
	Dyspepsia	1 (3.2)	0 (0.0)
	Flatulence	1 (3.2)	0 (0.0)
	Nausea	1 (3.2)	1 (3.4)
	Subjects with AEs	3 (9.7)	0 (0.0)
General disorders and administration site conditions	Fatigue	3 (9.7)	0 (0.0)
	Weakness	1 (3.2)	0 (0.0)
	Subjects with AEs	1 (3.2)	0 (0.0)
Hepatobiliary disorders	Hepatitis NOS	1 (3.2)	0 (0.0)
	Jaundice NOS	1 (3.2)	0 (0.0)
	Subjects with AEs	1 (3.2)	0 (0.0)
Infections and infestations	Tooth abscess	1 (3.2)	0 (0.0)
	Subjects with AEs	1 (3.2)	1 (3.4)
Investigations	Glucose urine present	0 (0.0)	1 (3.4)
	Liver function tests NOS abnormal	1 (3.2)	0 (0.0)
	Subjects with AEs	1 (3.2)	1 (3.4)
Metabolism and nutrition disorders	Appetite decreased NOS	1 (3.2)	0 (0.0)
	Hyperglycaemia NOS	0 (0.0)	1 (3.4)
	Subjects with AEs	2 (6.5)	3 (10.3)
Nervous system disorders	Dizziness	0	1 (3.4)
	Headache NOS	1 (3.2)	1 (3.4)
	Migraine NOS	0 (0.0)	1 (3.4)
	Paraesthesia	1 (3.2)	0 (0.0)
	Tremor	1 (3.2)	0 (0.0)
	Vertigo	0 (0.0)	1 (3.4)
	Subjects with AEs	2 (6.5)	0 (0.0)
Psychiatric disorders	Disturbance in attention	1 (3.2)	0 (0.0)
	Excitability	1 (3.2)	0 (0.0)
	Nervousness	1 (3.2)	0 (0.0)
	Subjects with AEs	1 (3.2)	0 (0.0)
Renal and urinary disorders	Difficulty in micturition	1 (3.2)	0 (0.0)
	Dysuria	1 (3.2)	0 (0.0)
	Subjects with AEs	1 (3.2)	0 (0.0)
Reproductive system and breast disorders	Postmenopausal hemorrhage	1 (3.2)	0 (0.0)
	Subjects with AEs	1 (3.2)	0 (0.0)
Skin and subcutaneous tissue disorders	Pruritus NOS	1 (3.2)	0 (0.0)
	Subjects with AEs	1 (3.2)	0 (0.0)
Surgical and medical procedures	Operation NOS	1 (3.2)	0 (0.0)

one dose of study medication. There was no significant difference between the two groups in the proportion of subjects reporting a TEAE (Fisher's exact test). The proportion of patients who experienced at least one TEAE was 10% (3 of 29) and 29% (9 of 31) in the placebo and the ocinaplon group, respectively. The incidence of TEAEs that were at least "remotely" related to study medication was 7% (2 of 29) for placebo and 19% (6 of 31) for ocinaplon.

Tabulation of AEs according to MedDRA System Organ Class (SOC) (Table 4) did not reveal a systematic difference in the distribution of TEAEs between groups. The low number of adverse events did not permit statistical analysis according to the individual categories of TEAEs. A visual inspection of Table 4 reveals no specific profile of treatment-emergent event preferred terms for ocinaplon compared to placebo treated patients. In terms of severity, the majority of TEAEs were classified as "mild." One

serious adverse event (SAE) occurred: a significant, elevation in liver enzymes followed by icterus in 1 patient dosed with ocinaplon. This SAE was considered by the investigator to be possibly related to the study medication. Transaminase levels at baseline were 10 μL ($<1 \times \text{ULN}$) and 9 μL ($<1 \times \text{ULN}$) for ALT and AST, respectively. Elevated ALT and AST levels were first observed in this patient after 3 weeks of double-blind treatment. Transaminase levels peaked 7 days after cessation of treatment (peak ALT was 1940 μL [$62.6 \times \text{ULN}$], and peak AST was 1600 μL [$51.6 \times \text{ULN}$]). An elevation in bilirubin with a peak level of 33 mg/dL was observed 21 days after treatment cessation. This subject showed continued decreases in these liver enzymes over time, and there were no sequelae. A full recovery was observed with no residual effects. A thorough evaluation of this SAE was performed along with liver enzyme data from the other subjects in this study. Analysis of plasma samples banked prior to study (taken after patients had fasted overnight from the predose sample on the first day of dosing) indicated that the subject with the SAE had marked elevations of 16 out of 23 amino acids (the elevations ranged between 2.2 and 18.7 times the lab upper limit of normal for the individual amino acids, respectively) assessed. In addition, the analysis of the above plasma samples revealed that the patient had a positive antinuclear antibody titer, suggesting an underlying autoimmune process that existed at the time the patient entered the trial. The patient was on a vegetarian diet, and had a body mass index (BMI) of 20.9 kg/m^2 (at the lower end of the normal range for the patient's age [45 years]).

Despite these factors that could have potentially either produced or contributed to the exacerbation of the liver enzyme elevations, the etiology of the jaundice and elevated transaminase levels in this patient remains unclear. An analysis of liver enzyme increases in the remaining subjects indicated no statistically significant differences between the ocinaplon and placebo groups when comparing the pretreatment baseline to the peri- or posttreatment periods. In both groups, the proportion of patients with elevated liver enzyme values remained essentially unchanged during the treatment period as compared to the predose baseline (McNemar's exact test for change; ocinaplon group: $S = 0.1$, $df = 1$, n.s.; placebo group: $S = 1$, $df = 1$, n.s.).

At baseline prior to any dosing, the proportion of subjects with abnormal liver values was 6.9% (2/29) in the placebo and 19.3% (6/31) in the ocinaplon group, respectively. During the double-blind treatment and discontinuation phase of the trial, the proportion of subjects who showed an elevation in the liver enzyme values was 10.3% (3 of 29 patients) in the placebo and 16.1% (5 of 31 patients) in the ocinaplon group, respectively. In addition

to the previously described SAE, there was one subject in both the placebo and ocinaplon groups whose liver enzyme elevations were considered by the investigator as "clinically significant." For the patient in the ocinaplon group, the increases (in ALT and AST) occurred after the cessation of dosing; and the patient subsequently admitted to ingesting kava kava, a herbal preparation associated with an increased risk for liver abnormalities [38].

Discussion

Analysis of the primary efficacy parameter, change in the total HAM-A scale score over time, demonstrated that treatment with ocinaplon produces a significant and rapid reduction in anxiety symptoms compared to placebo. Parallel improvements were observed on secondary outcome measures, including the patient self-rating scale and global evaluation and the clinician's clinical global impression. Since self-rating scales may offer more direct insight into the inner suffering and psychological distress of patients with GAD than assessments by an external rater, it is of interest that among all secondary measures, the self-rating scale for anxiety showed the most pronounced separation between ocinaplon and placebo treatment. This result is consistent with Bourin's observation [39] that during clinical testing of anxiolytic drugs, anxiety self-rating scales are advantageous in that they reduce the variability associated with an external assessor.

In order to better understand the ocinaplon-placebo difference in terms of potential clinical importance, the effect size was computed versus placebo. To facilitate comparison with other studies, we used last observation carried forward (LOCF) estimates, since such estimates are traditionally reported in the literature. The LOCF estimates for the improvement on the total score of the HAM-A scale indicated a difference of 6 points between ocinaplon and placebo, and the statistical effect size index was 0.68 (0.3, 0.5, 0.8 are small, medium, and large [36], respectively). In general, clinical trials of anxiolytics report an approximately 3-point difference on total score of the HAM-A scale between active and placebo (range is between 2 and 4 points). Recent clinical trials of anxiolytics reported an effect size of less than 2 points for paroxetine [13]; 2.5 points for escitalopram [12]; 3.4 points for pregabalin [40], and 2.5 points for sertraline [41], respectively, following 4 weeks of treatment.

The CCG-I scores were used to determine the percentage of study population who demonstrated clinical improvement, defined as a rating of "very much improved" or "much improved" [13,37]. By the end of the double-blind phase of the trial, the estimated rate of clinical

improvement was more than twice as high, in the ocinaplon compared to the placebo group (74% and 35%), respectively. The magnitude of the effect in the placebo arm may be a key determinant of whether a study yields a positive outcome. Therefore, the robust effect of ocinaplon is noteworthy in light of the effect magnitude in the placebo group (35% response rate, 4.5 points improvement) which is consistent with other published data [12,41,42].

Pharmacological agents appear to produce a varying profile of response to different symptoms of anxiety. In particular, BZs have been reported to be more beneficial for the somatic symptoms of anxiety [8] Buspirone and antidepressants are considered more effective in reducing the psychic and far less so in treating somatic symptoms of anxiety [11,43]. In the present study, ocinaplon produced a significant improvement on both the somatic and psychic factors subscales of the HAM-A relative to placebo. This finding is particularly relevant from a clinical standpoint, since as noted by Meoni [44]: "Although the most prominent feature of GAD is chronic worry and its psychic manifestations, patients suffering from GAD are more likely to visit a physician because of somatic symptoms and sleep impairments related to anxiety and the control of such symptoms may therefore become the principal focus of the treatment."

The observation that a significant improvement in the HAM-A was present as observed as early as after 1 week of ocinaplon treatment has important clinical implications. Thus, many anxiolytics, including SSRIs, SNRIs, and buspirone, typically have a much longer delay prior to the development of beneficial therapeutic effects [8,9]. Such a delayed onset may not only contribute to non-compliance, but can exacerbate symptoms such as restlessness and nervousness after initiating dosing. Thus, when an immediate relief of symptoms is needed, BZs (either alone or combined with antidepressants) are often prescribed despite their obvious limitations [9,10]. From a pharmacological perspective, the observation that ocinaplon, a GABA_A receptor modulator [24], appears to rapidly alleviate anxiety symptoms, is consistent with the clinical effects of BZs which also act on the GABA_A receptor complex [6]. This clinical finding, if confirmed in additional studies, will offer an advantage over biogenic-amine based agents used in the treatment of GAD.

Rapid discontinuation of anxiolytics, particularly BZs, can lead to a withdrawal syndrome that can pose a significant challenge for the physician. To explore whether a relatively rapid tapering of ocinaplon is clinically feasible and well tolerated, the study design included a 1-week tapering off period. The results support the relative ease and safety of a rapid 1-week taper of medication following 4 weeks of treatment because no treatment-

emergent adverse events were detected in the ocinaplon group. Since the length of treatment may be an important factor in the emergence of potential rebound, withdrawal, and discontinuation effects reported with various anxiolytics, the analyses were repeated in the subset of subjects completing the 28-day treatment. This duration is similar to what has been suggested as a threshold criterion (≥ 30 days) for the development of the selective serotonin reuptake inhibitor discontinuation syndrome [45]. The change in HAM-A scores was minimal in this subset of patients, with an approximately 1-point increase in both groups. Within the framework of both the relatively small sample size and the duration of the trial, these results suggest that a rapid taper of ocinaplon is clinically feasible, with no rebound or withdrawal effects.

Ocinaplon was well tolerated in this study, with an overall rate of discontinuation not different from placebo. Only 4 patients (13%) in the ocinaplon and 4 patients (10.3%) in the placebo group reported treatment emergent AEs in the Nervous System and Psychiatric MedDRA System/Organ classes combined. Moreover, the incidence of nausea and headache, which frequently occur with SSRI or SNRI medications [12,13,16], was low, and ocinaplon treatment was not associated with an increased likelihood of these AEs compared to placebo. Perhaps most striking was the lack of BZ-like AEs with ocinaplon [46]. Thus, there was no indication of a clinically meaningful increase of such effects (sedation, ataxia, or cognitive deficits) by ocinaplon, with only 1 patient in the active group who exhibited "Disturbance in attention." These safety findings are consistent with the anxiolytic profile of ocinaplon in both preclinical models [20,24] and both single and multiple ascending dose safety and tolerability studies in humans.

The only SAE in the ocinaplon group that was considered to be possibly related to the study medication was marked transaminase elevations followed by jaundice. Although several preexisting factors including multiple hyperaminoacidemias, potential nutritional deficiencies with a vegetarian diet, low BMI, and autoimmune disorder could have either produced or contributed to this profile, the etiology remains uncertain. Further investigation is needed to determine whether any relationship exists between the study drug and liver enzyme elevations.

In conclusion, this study demonstrates that ocinaplon is an effective and well-tolerated anxiolytic in patients with moderate-to-severe generalized anxiety disorder. The results are consistent with a rapid onset of action and a reduction in both psychic and somatic symptoms of anxiety. These results are consistent with both preclinical and preliminary human studies [20,24] suggesting that ocinaplon is an anxiolytic agent that, like BZs,

produces its pharmacological actions via an activation of GABAA receptors [20,24]. Nonetheless, the precise molecular mechanism(s) by which selective anxiolytic action is likely to be produced in both preclinical and clinical studies requires further investigation [47].

Furthermore, caution should be exercised while interpreting the above findings. The study was a pilot trial (total N = 60) with a short duration (4 weeks), which does not allow making inferences on the longer-term efficacy of ocinaplon. The high rate of noncompletion raises questions about potential biases with regard to using the HLM approach to evaluate outcomes. We note, however, that ANCOVA yielded results similar to those of the HLM; moreover, the noncompletion occurred primarily due to the early termination of the trial, and its rate was similar in the active and placebo groups.

The fact that a score of ≤ 15 on the Ham-D (17 items) was used for excluding comorbid major depressive disorder (MDD) is an additional limitation of the study. In particular, this threshold is still compatible with mild-to-moderate depression, and therefore the potential presence of subsyndromal MDD serves as an additional caveat from the perspective of interpreting the results in the context of anxi selectivity. Additional clinical trials directly comparing ocinaplon or a similar molecule to a benzodiazepine, and addressing the above limitations, will provide a stringent/robust test of the hypothesis that this molecule is anxi selectivity. Further studies to evaluate the efficacy and safety of ocinaplon treatment in generalized anxiety disorder are warranted.

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Author Contribution

Drs. Beer and Lipka designed the study, developed the study protocol, and participated in the generation of the manuscript. Dr. Czobor developed the statistical design, conducted the statistical analyses, and produced the first draft of the manuscript. Dr. Skolnick provided conceptual oversight over the entire project and assisted Dr. Czobor with the interpretation of results and preparation of this manuscript. All authors contributed to and approved to the manuscript, which has not been published before and is not under consideration for publication elsewhere.

Conflict of Interest

All authors were either former or are current employees of Dov Pharmaceutical, Inc. Dov Pharmaceutical served as a sponsor for the study.

References

1. Sartorius N, Ustun TB, Lecrubier Y, Wittchen HU. Depression comorbid with anxiety: Results from the WHO study on psychological disorders in primary health care. *Br J Psychiatry Suppl* 1996;**30**:38–43.
2. Wittchen HU, Hoyer J. Generalized anxiety disorder: Nature and course. *J Clin Psychiatry* 2001;**62**(Suppl 11): 15–19.
3. Roy-Byrne PP, Katon W. Generalized anxiety disorder in primary care: The precursor/modifier pathway to increased health care utilization. *J Clin Psychiatry* 1997;**58**(Suppl 3):34–38.
4. Roy-Byrne PP. Generalized anxiety and mixed anxiety-depression: Association with disability and health care utilization. *J Clin Psychiatry* 1996;**57**(Suppl 7):86–91.
5. Atack JR. Anxi selectivity compounds acting at the GABA(A) receptor benzodiazepine binding site. *Curr Drug Targets CNS Neurol Disord* 2003;**2**:213–232.
6. Barnard EA, Skolnick P, Olsen RW, et al. International Union of Pharmacology. XV. Subtypes of gamma-aminobutyric acidA receptors: Classification on the basis of subunit structure and receptor function. *Pharmacol Rev* 1998;**50**:291–313.
7. Whiting PJ. GABA-A receptors: A viable target for novel anxiolytics? *Curr Opin Pharmacol* 2006;**6**:24–29.
8. Goodman WK. Selecting pharmacotherapy for generalized anxiety disorder. *J Clin Psychiatry* 2004;**65**(Suppl 13):8–13.
9. Nash JR, Nutt DJ. Pharmacotherapy of anxiety. In: Sibley DR, Hanin I, Kuhar MJ, Skolnick P, editors. Handbook of contemporary neuropharmacology. Vol. 2. Hoboken, NJ: John Wiley & Sons, Inc., 2007:59–91.
10. Stahl SM. Don't ask, don't tell, but benzodiazepines are still the leading treatments for anxiety disorder. *J Clin Psychiatry* 2002;**63**:756–757.
11. Rickels K, Downing R, Schweizer E, Hassman H. Antidepressants for the treatment of generalized anxiety disorder. A placebo-controlled comparison of imipramine, trazodone, and diazepam. *Arch Gen Psychiatry* 1993;**50**:884–895.
12. Davidson JR, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: Double-blind, placebo controlled, flexible-dose study. *Depress Anxiety* 2004;**19**:234–240.
13. Pollack MH, Zaninelli R, Goddard A, McCafferty JP, Bellew KM, Burnham DB, Iyengar MK. Paroxetine in the

- treatment of generalized anxiety disorder: Results of a placebo-controlled, flexible-dosage trial. *J Clin Psychiatry* 2001;**62**:350–357.
14. Laakmann G, Schule C, Lorkowski G, Baghai T, Kuhn K, Ehrentauf S. Buspirone and lorazepam in the treatment of generalized anxiety disorder in outpatients. *Psychopharmacology (Berl)* 1998;**136**:357–366.
 15. Montgomery SA, Mahe V, Haudiquet V, Hackett D. Effectiveness of venlafaxine, extended release formulation, in the short-term and long-term treatment of generalized anxiety disorder: Results of a survival analysis. *J Clin Psychopharmacol* 2002;**22**:561–567.
 16. Sheehan DV. Venlafaxine extended release (XR) in the treatment of generalized anxiety disorder. *J Clin Psychiatry* 1999;**60**(Suppl 22):23–28.
 17. Davidson JR, DuPont RL, Hedges D, Haskins JT. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. *J Clin Psychiatry* 1999;**60**:528–535.
 18. Thase ME. Effects of venlafaxine on blood pressure: A meta-analysis of original data from 3744 depressed patients. *J Clin Psychiatry* 1998;**59**:502–508.
 19. Johnstone TB, Hogenkamp DJ, Coyne L, et al. Modifying quinolone antibiotics yields new anxiolytics. *Nat Med* 2004;**10**:31–32.
 20. Basile AS, Lippa AS, Skolnick P. Anxiolytic: Can less be more? *Eur J Pharmacol* 2004;**500**:441–451.
 21. Lippa AS, Coupet J, Greenblatt EN, Klepner CA, Beer B. A synthetic non-benzodiazepine ligand for benzodiazepine receptors: A probe for investigating neuronal substrates of anxiety. *Pharmacol Biochem Behav* 1979;**11**:99–106.
 22. Ballenger JC, McDonald S, Noyes R Jr, et al. The first double-blind, placebo-controlled trial of a partial benzodiazepine agonist, abecarnil (ZK 112–119), in generalized anxiety disorder. *Adv Biochem Psychopharmacol* 1992;**47**:431–447.
 23. van Steveninck AL, Gieschke R, Schoemaker RC, et al. Pharmacokinetic and pharmacodynamic interactions of bretazenil and diazepam with alcohol. *Br J Clin Pharmacol* 1996;**41**:565–573.
 24. Lippa A, Czobor P, Stark J, et al. Selective anxiolysis produced by ocinaplon, a GABA(A) receptor modulator. *Proc Natl Acad Sci U S A* 2005;**102**:7380–7385.
 25. de Haas SL, de Visser SJ, Van Der Post JP, et al. Pharmacodynamic and pharmacokinetic effects of MK-0343, a GABA(A) $\alpha_2\beta_3$ subtype selective agonist, compared to lorazepam and placebo in healthy male volunteers. *J Psychopharmacol* 2008;**22**:24–32.
 26. Vogel JR, Beer B, Clody DE. A simple and reliable conflict procedure for testing anti-anxiety agents. *Psychopharmacologia* 1971;**21**:1–7.
 27. Lippa A, Nash P, Greenblatt E. Pre-clinical neuropsychopharmacological testing procedures for anxiolytic drugs. In: Fielding S, Lal H, editors. *Industrial pharmacology. Anxiolytics ed.*, Vol. 3. Mt. Kisco, NY: Futura Publishing Co., 1979;41–81.
 28. Czobor P, Stark J, Beer G, Beckett S, Dietrich B, Lippa A. A double-blind, placebo controlled study of DOV 273,547 (Ocinaplon) in the treatment of Generalized Anxiety Disorder (GAD). 33rd Annual Meeting of the Society of Neuroscience, Abstract No. 959.12, New Orleans, LA: USA, 2003.
 29. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959;**23**:50–55.
 30. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, Fourth Edition. 4th ed., Washington, DC: American Psychiatric Association, 1994.
 31. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry* 1960;**23**:56–62.
 32. Guy W. ECDEU assessment manual for psychopharmacology. Revised. Rockville, MD: National Institute of Mental Health, 1976.
 33. Bryk AS, Raudenbush SW. Hierarchical linear models: applications and data analysis methods. Newbury Park: Sage Publications, 1992.
 34. Gibbons RD, Hedeker D, Waternaux C, Davis JM. Random regression models: A comprehensive approach to the analysis of longitudinal psychiatric data. *Psychopharmacol Bull* 1988;**24**:438–443.
 35. Bryk AS, Raudenbush SW. Application of hierarchical linear models to assessing change. *Psychol Bull* 1987;**101**:147–158.
 36. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale: Lawrence Erlbaum Associates, Inc., 1988.
 37. Rickels K, Mangano R, Khan A. A double-blind, placebo-controlled study of a flexible dose of venlafaxine ER in adult outpatients with generalized social anxiety disorder. *J Clin Psychopharmacol* 2004;**24**:488–496.
 38. Cloutier DL. Kava kava: Examining new reports of toxicity. *Toxicol Lett* 2004;**150**:85–96.
 39. Bourin M. Clinical testing of anxiolytic drugs. Clinical testing of anxiolytic drugs. In: Griez EJL, Faravelli C, Nutt D, Zohar J, editors. *Anxiety Disorders*. Chichester, West Sussex: John Wiley & Sons, Ltd., 2001;325–337.
 40. Pande AC, Crockatt JG, Feltner DE, et al. Pregabalin in generalized anxiety disorder: A placebo-controlled trial. *Am J Psychiatry* 2003;**160**:533–540.
 41. Allgulander C, Dahl AA, Austin C, et al. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. *Am J Psychiatry* 2004;**161**:1642–1649.
 42. Feltner DE, Crockatt JG, Dubovsky SJ, et al. A randomized, double-blind, placebo-controlled, fixed-dose, multicenter study of pregabalin in patients with generalized anxiety disorder. *J Clin Psychopharmacol* 2003;**23**:240–249.

43. Rickels K, Schweizer E. The clinical presentation of generalized anxiety in primary-care settings: Practical concepts of classification and management. *J Clin Psychiatry* 1997;**58**(Suppl 11):4–10.
44. Meoni P, Hackett D, Lader M. Pooled analysis of venlafaxine XR efficacy on somatic and psychic symptoms of anxiety in patients with generalized anxiety disorder. *Depress Anxiety* 2004;**19**:127–132.
45. Black K, Shea C, Dursun S, Kutcher S. Selective serotonin reuptake inhibitor discontinuation syndrome: Proposed diagnostic criteria. *J Psychiatry Neurosci* 2000;**25**:255–261.
46. Gorman JM. Treating generalized anxiety disorder. *J Clin Psychiatry* 2003;**64**(Suppl 2):24–29.
47. Basile AS, Lippa A, Skolnick P. GABA_A receptor modulators as anxiolytic agents. *Drug Discov Today Ther Strateg* 2006;**3**:475–481.