European Neuropsychopharmacology (2012) **22**, 847–857

www.elsevier.com/locate/euroneuro

Vortioxetine (Lu AA21004) in generalized anxiety disorder: Results of an 8-week, multinational, randomized, double-blind, placebo-controlled clinical trial

Leszek Bidzan[a], Atul R. Mahableshwarkar[b], Paula Jacobsen[b], Mingjin Yan[b], David V. Sheehan[c,*]

[a]*Department of Developmental, Psychotic, and Geriatric Psychiatry, Medical University of Gdansk, Gdańsk, Poland*
[b]*Takeda Global Research & Development Inc., Deerfield, IL, USA*
[c]*University of South Florida, College of Medicine, Tampa, FL, USA*

Received 2 April 2012; received in revised form 20 June 2012; accepted 19 July 2012

KEYWORDS
Generalized anxiety disorder (GAD);
Multimodal;
Bis-aryl-sulfanyla-mine;
Major depressive disorder (MDD)

Abstract
Vortioxetine is a multimodal antidepressant, with anxiolytic properties observed in preclinical studies. The goal of the current study was to evaluate the efficacy and tolerability of vortioxetine 5 mg vs placebo in adults with generalized anxiety disorder (GAD). Adults with a primary diagnosis of GAD (HAM-A total score $\geq$20 and MADRS score $\leq$16) received vortioxetine 5 mg or placebo for 8 weeks. The primary efficacy endpoint was reduction in HAM-A total scores from baseline after 8 weeks of treatment compared with placebo. Key secondary measurements were HAD anxiety subscore, CGI-I, SDS total score, HAM-A response rates, HAM-A total score for subjects whose baseline HAM-A total score was $\geq$25, and SF-36 social functioning subscore. HAM-A remission rates were also measured. Adverse events (AEs) were assessed throughout the study. In total, 301 subjects (mean age, 45.2 years; 31% male) were randomized (1:1) to receive vortioxetine 5 mg (n=150) or placebo (n=151). After 8 weeks of treatment, there was a statistically significant difference in reduction from baseline in HAM-A total score for the vortioxetine group (−14.30) compared with placebo recipients (−10.49) ($P<0.001$). Statistically significant differences were observed for all key secondary outcomes favoring vortioxetine treatment (vs placebo), using a mixed model for repeated measurements (MMRM) analysis. Active treatment resulted in a significantly higher rate of remission. Vortioxetine was well tolerated. The most common treatment-related AEs were nausea, headache, dizziness, and dry mouth. In sum, vortioxetine was safe and effective in treating adults with GAD in this multinational population.

*Corresponding author.
E-mail address: dsheehan@health.usf.edu (D.V. Sheehan).

0924-977X/$ - see front matter © 2012 Elsevier B.V. and ECNP. All rights reserved.
http://dx.doi.org/10.1016/j.euroneuro.2012.07.012

1. Introduction

Generalized anxiety disorder (GAD) is a common psychiatric condition that has detrimental effects on patient functioning. In the European Union, the 12-month prevalence of GAD is estimated to range from 1.7% among individuals aged 14-65 years to 3.4% in older persons (Wittchen et al., 2011). In the United States (US), the 12-month prevalence of GAD is approximately 3.1% (Kessler et al., 2005). Individuals with GAD often have psychiatric and medical comorbidities that make it difficult to determine the personal and societal impact of their anxiety symptoms. However, a data analysis from the German National Health Interview and Examination Survey Mental Health Supplement found that compared with controls, individuals with GAD were significantly more likely to report substantially reduced overall activity, and to have SF-36 mental component summary scores indicative of impairment (Hoffman et al., 2008). A recent large European study of outpatients with GAD found that residual functional impairment remains a problem for many individuals with GAD (Bobes et al., 2011). Although benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and atypical antipsychotic medications are effective in treating anxiety symptoms in some people, between 25% and 40% of subjects evaluated in clinical trials remain symptomatic (Baldwin, et al., 2011a). In addition, side effects limit the use of benzodiazepines (Baldwin et al., 2011a), atypical antipsychotics, and SSRIs (Baldwin et al., 2011a). Given the incomplete response and side effects associated with existing treatments, there remains a need for more effective and safer interventions to reduce the impact of GAD.

Vortioxetine is an investigational multimodal antidepressant that is believed to work through a combination of two pharmacological modes of action: serotonin (5-HT) reuptake inhibition and 5-HT receptor activity (Bang-Andersen et al., 2011). Preclinical studies have found that vortioxetine functions as a 5-HT_3 and 5-HT_7 receptor antagonist, a 5-HT_{1A} receptor agonist, a 5-HT_{1B} receptor partial agonist, and an inhibitor of the 5-HT transporter in vitro. In vivo nonclinical studies have demonstrated that vortioxetine raises the levels of the neurotransmitters 5-HT, norepinephrine, dopamine, acetylcholine, and histamine in the ventral hippocampus and the median prefrontal cortex of the brain (Bang-Andersen et al., 2011; Mørk et al., 2011). Vortioxetine has demonstrated activity in validated animal models predictive of anxiolytic activity (Mørk et al., 2011).

In three multinational, randomized, placebo-controlled trials in subjects with MDD, vortioxetine 10 mg was reportedly effective as an antidepressant (Alvarez et al., 2011; Henigsberg et al., 2011; Baldwin et al., 2011b). In a fourth trial, conducted in the US, vortioxetine 5 mg did not differ significantly from placebo in reducing the depressive symptoms of major depressive disorder (MDD) (Jain et al., submitted for publication). In all four studies, vortioxetine was safe and well tolerated, with nausea, headache, dizziness, and dry mouth being the most frequently reported drug-related adverse events (AEs).

In a proof of concept trial (Alvarez et al., 2011), patients with MDD who were randomized to receive vortioxetine 5 mg or 10 mg experienced a greater reduction in Baseline Hamilton Rating Scale for Anxiety (HAM-A) total scores (Hamilton, 1959) after 3 weeks of treatment compared with those receiving placebo, and the differences were statistically significant. The vortioxetine groups continued to show significantly greater reductions in this secondary end point relative to placebo across the 6 weeks of study treatment (difference from placebo was −3.3 with vortioxetine 5 mg; −3.0 with vortioxetine 10 mg, $P<0.01$ for both comparisons using Last Observation Carried Forward). Based on this finding and other preliminary data, two studies of identical design were conducted simultaneously as part of the vortioxetine development program. The objective of the randomized, placebo-controlled studies was to evaluate the efficacy and tolerability of vortioxetine 5 mg in patients with GAD. The study examined change from baseline in HAM-Atotal scores and global measures such as the Clinical Global Impression of Improvement (CGI-I) (Guy, 1976), which are traditional efficacy endpoints for clinical trials of GAD. Change in baseline scores on the Sheehan Disability Scale (SDS) (Leon et al., 1997) and the social functioning subscore of the 36-Item Short-Form Health Survey (SF-36) (Ware and Sherbourne, 1992) were included as endpoints in this study to address the impact of treatment on functional aspects of GAD. The results of the second GAD trial are reported in a paper by Rothschild et al. (in preparation).

2. Experimental procedures

2.1. Study design

This phase III, multinational, randomized, parallel-group, placebo-controlled, fixed-dose, 8-week trial was conducted at 47 sites in Estonia, Germany, Latvia, Lithuania, Poland, Romania, Russia, Ukraine, and South Africa. Subjects were randomized within 1 week of screening. Evaluation visits occurred every week for the first 2 weeks of treatment, then every 2 weeks for the remainder of the 8-week treatment period. The study was conducted in accordance with the principles of Good Clinical Practice (ICH, 1996) and the Declaration of Helsinki (World Medical Association (WMA), 2008). Local research Ethics Committees approved the trial design, and eligible patients provided written informed consent before participating in the trial.

2.2. Study population

Men and nonpregnant women ≥18 years of age were considered eligible if they had a primary diagnosis of GAD according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition Text Revision (DSM-IV-TR) (classification code 300.02) (American Psychiatric Association, 2000), as well as a HAM-A total score ≥20 at screening and baseline, HAM-A score ≥2 on both Item 1 (anxious mood) and Item 2 (tension) at screening and baseline, and a Montgomery and Åsberg (1979) Depression Rating Scale (MADRS) total score ≤16 at screening and baseline.

Individuals were excluded from participation if they had any current psychiatric disorder other than GAD, as defined in the DSM-IV-TR (as assessed by the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998). Additional exclusion criteria were a current diagnosis or history of a manic or hypomanic episode, schizophrenia, or any other psychotic disorder, including major depression with psychotic features, mental retardation, organic mental disorder, or mental disorder due to a general medical condition, as defined in the DSM-IV-TR. Also excluded were subjects who had a substance use disorder (except nicotine and caffeine) within the previous 6 months, as defined in the DSM-IV-TR;

presence or history of a clinically significant neurological disorder (e.g., epilepsy); a neurodegenerative disorder (Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington disease, etc.); or any Axis II disorder that might compromise the study. Subjects who were considered by the investigator to pose a significant risk of suicide, and those who had a score $\geq$5 on Item 10 (suicidal thoughts) on the MADRS or had made a suicide attempt in the previous 6 months, were excluded from participation. Also ineligible were any subjects that, in the investigator's judgment, had failed to respond to adequate treatment with an SSRI and/or SNRI.

2.3. Study treatments

Eligible subjects were randomized (1:1) to receive 5 mg of vortioxetine orally or placebo, once daily, during the 8-week double-blind treatment period. Placebo consisted of lactose monohydrate and magnesium stearate encapsulated in oval brownish-orange capsules identical to those containing the active study drug. An interactive voice-response system (IVRS) was used to manage the dispensation of study medication, and all participants were blinded to treatment assignment throughout the study.

2.4. Efficacy measures

Prior to randomization, baseline measurements were obtained for the HAM-A, Clinical Global Impression-Severity (CGI-S) of illness scale, patient-reported Hospital Anxiety and Depression (HAD) scale (Zigmond and Snaith, 1983), SF-36, and the SDS. HAM-A, CGI-S, and CGI-I were measured at every evaluation visit.

2.5. Safety measures

AEs were recorded at each visit, with investigators determining the AE severity and its relationship to the study drug. Physical examinations were performed at screening and Week 8. Weight was measured at screening, baseline, Week 4, and Week 8. Vital signs were monitored at every visit. Clinical laboratory tests (hematology, serum chemistry, and urinalysis) and 12-lead electrocardiograms (ECGs) were performed at baseline, Week 4, and Week 8 (or study completion/withdrawal), in addition to the screening visit. The Columbia-Suicide Severity Rating Scale (C-SSRS) (Posner et al., 2007) was administered at each visit in order to monitor and assess potential suicidality throughout the study.

2.6. Other measures

Other measures were assessed as follows: HAD at Weeks 1, 4, and 8; SF-36 at Weeks 2, 4, and 8; and SDS at Weeks 1, 2, 4, and 8.

2.7. Statistical analysis

Analysis sets: The safety set comprised all subjects who were randomized and received at least one dose of study medication. The full analysis set (FAS) included all subjects who were randomized, received at least one dose of study medication, and had at least one valid post-baseline value for the primary assessment.

2.8. Statistical methods

The primary efficacy endpoint, as prespecified in the protocol, was the change from baseline in HAM-A total score at 8 weeks of treatment. Comparisons between vortioxetine 5 mg and placebo were performed on the FAS at all assessment points, using a mixed model for repeated measurements (MMRM). To confirm the results of the primary analysis (MMRM), the change from baseline in HAM-A total score after 8 weeks (primary endpoint) was also analyzed using analysis of covariance (ANCOVA), with treatment and center as fixed factors and baseline HAM-A total score as covariate, and based on last observation carried forward (LOCF) and observed cases (OC; i.e., only values actually measured at that time point) data sets. Change from baseline in the HAD anxiety subscale, HAD depression subscale, and SF-36 domain subscores served as secondary endpoints; these were analyzed as continuous variables (MMRM on OC; ANCOVA on LOCF and OC) in a manner similar to that used to evaluate the primary endpoint. The relevant baseline value was used as the covariate adjustment in the MMRM and ANCOVA analyses.

CGI-S and CGI-I also were analyzed as continuous variables (MMRM on OC; ANCOVA on LOCF and OC), as described for the primary variable, with baseline CGI-S used as the covariate adjustment in the MMRM and ANCOVA analyses of CGI-I.

HAM-A response (defined as a decrease of $\geq$50% from baseline in HAM-A total score) and remission (defined as a HAM-A total score of $\leq$7) were analyzed at all time points by logistic regression, adjusting for baseline score and treatment using both LOCF and OC data.

Effect sizes were calculated using mean values for vortioxetine 5 mg and placebo, with the difference divided by the pooled standard deviation. To control the type I error at the level of 0.05, the primary endpoint and the six key secondary endpoints were tested in a prespecified sequential order, as follows:

1. Change from baseline in HAM-A total score at Week 8 (MMRM).
2. Change from baseline in HAD anxiety subscore at Week 8 (MMRM).
3. CGI-I at Week 8 (MMRM).
4. Change from baseline in SDS total score at Week 8 (MMRM).
5. HAM-A response rate at Week 8 (LOCF).
6. Change from baseline in HAM-A total score at Week 8 in the subgroup of subjects with HAM-A total score $\geq$25 (MMRM) at baseline.
7. Change from baseline in SF-36 social functioning subscore at Week 8 (MMRM).

As soon as the result for a given endpoint was found not significant at the.05 level, the testing procedure was stopped for all subsequent endpoints. Nominal *P* values, with no adjustment for multiplicity, were reported for endpoints not included in the hierarchy or were reported after a result proved not significant. The phrase "separation from placebo" was used to describe findings with nominal *P* values $\leq$0.5.

The numbers needed to treat (NNT) were calculated as the inverse of the absolute risk reduction over 8 weeks for response and remission rates.

AEs were coded by system organ class (SOC) and preferred term (PT) using the *Medical Dictionary for Regulatory Activities* (MedDRA) Version 11.1. The incidences of all AEs were summarized descriptively.

3. Results

3.1. Subjects

The study began in September 2008 and concluded in June 2009. The disposition of subjects is shown in Figure 1. Of the 375 subjects who were screened, 301 were randomized to treatment. The safety set comprised 300 subjects; one person in the placebo group did not receive any study medication. Demographic and baseline characteristics were

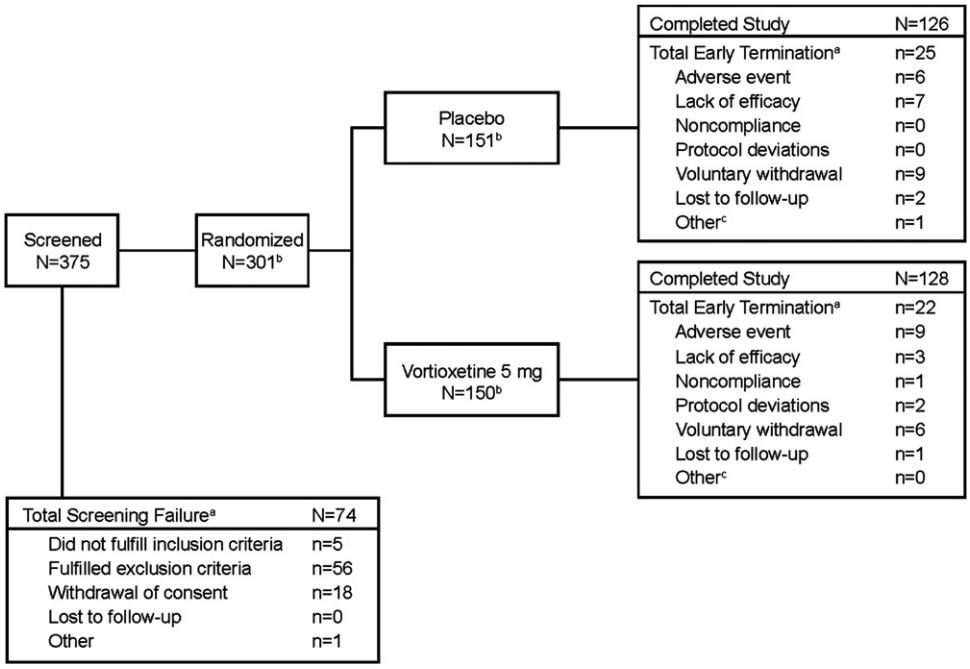

Figure 1 CONSORT diagram.

Table 1 Demographics and baseline characteristics.

Characteristic	Study group	
	Placebo ($n=151$)	Vortioxetine 5 mg ($n=150$)
Gender		
Male, *n* (%)	58 (38.4)	47 (31.3)
Age (yr), mean (SD)	45.3 (13.5)	45.0 (14.1)
Caucasian race (white, including Hispanic), *n* (%)	151 (100)	150 (100)
Ethnicity		
Hispanic/Latino, *n* (%)	8 (5.3)	5 (3.3)
Duration of current GAD (mo)		
Median (range)	7.5 (1–120)	8.0 (1–77)
Previously treated for GAD, *n* (%)	61 (40.7)	69 (46.0)
Previously treated with medication, *n* (%)	60 (40.0)	67 (44.7)
Previously treated with an SSRI, *n* (%)	26 (17.3)	30 (20.0)
HAM-A total score		
Mean (SD)	26.8 (4.0)	26.3 (3.9)
HAM-A ≥ 25, *n* (%)	100 (66.2)	96 (64.0)
CGI-S, LS mean (SE)	4.5 (0.7)	4.5 (0.7)
SDS total score, LS mean (SE)	17.54 (0.562)	17.80 (0.589)

Abbreviations: GAD, generalized anxiety disorder; HAM-A, Hamilton Anxiety Scale; CGI-S, Clinical Global Impression-Severity of illness scale; SDS, Sheehan Disability Scale; LS, least squares.

comparable for the two study groups (Table 1). Less than half of each study group had been treated previously for GAD. Almost all of the previously treated subjects had received medication for the treatment of GAD (60 of 61 subjects in the placebo group; 67 of 69 subjects in the vortioxetine group). Of those individuals, approximately half had been treated with an SSRI (26 subjects in the placebo group; 30 subjects in the vortioxetine group). The median duration of current GAD was 7.5 months (range, 1–120 months) in the placebo group and 8.0 months (range, 1–77 months) in the active-treatment arm.

3.2. Primary efficacy outcomes

With respect to the primary efficacy endpoint, there was a statistically significant difference between vortioxetine and placebo (Table 2). The least squares (LS) mean change from

Table 2 Primary efficacy endpoint and key secondary efficacy variables at Week 8.

	MMRM on FAS		ANCOVA LOCF	
	Placebo (*n* = 151)	**Vortioxetine 5 mg (*n* = 150)**	**Placebo (*n* = 151)**	**Vortioxetine 5 mg (*n* = 150)**
Primary efficacy endpoint				
HAM-A total score				
Baseline *n* value	148	149	148	149
Baseline LS mean (SE)	26.8 (4.0)	26.3 (3.9)	26.69 (0.310)	26.50 (0.307)
Change from baseline to Week 8				
n	126[a]	128[a]	148	149
LS mean (SE)	−10.49 (0.69)	−14.30 (0.69)	−9.59 (0.706)	−13.43 (0.700)
P value		<0.001		<0.001
LS mean difference from placebo (SE)		−3.81 (0.98)		−3.84 (0.973)
95% CI		(−5.74, −1.88)		(−5.75, −1.92)
Effect size[d]		0.55		
Key secondary variables				
HAD anxiety subscore				
Baseline *n* value	148	149	148	149
Baseline LS mean (SE)	14.68 (0.231)	14.20 (0.229)	14.68 (0.231)	14.20 (0.229)
Change from baseline to Week 8				
n	128[a]	129[a]	148	149
LS mean (SE)	−4.20 (0.396)	−6.49 (0.393)	−4.05 (0.393)	−6.11 (0.386)
P value		<0.001		<0.001
LS mean difference from placebo (SE)		−2.30 (0.555)		−2.07(0.539)
95% CI		(−3.39, −1.20)		(−3.13, −1.01)
Effect size[d]		0.47		
CGI-I score[b]				
Baseline *n* value	148	149	148	149
Baseline LS mean (SE)	4.49 (0.047)	4.49 (0.047)	4.49 (0.047)	4.49 (0.047)
Score at Week 8				
n	126[a]	128[a]	148	149
LS mean (SE)	2.66 (0.098)	2.19 (0.098)	2.78 (0.101)	2.35 (0.101)
P value		<0.001		<0.002
LS mean difference from placebo (SE)		−0.46 (0.138)		−0.43 (0.140)
95% CI		(−0.73, −0.19)		(−0.70, −0.15)
Effect size[d]		0.49		
SDS total score				
Baseline *n* value	124	120	124	120
Baseline LS mean (SE)	17.54 (0.562)	17.80 (0.589)	17.54 (0.562)	17.80 (0.589)
Change from baseline to Week 8				
n	109[a]	102[a]	124	120
LS mean (SE)	−6.14 (0.631)	−8.10 (0.656)	−5.66 (0.653)	−7.15 (0.686)
P value		0.031		0.102
LS mean difference from placebo (SE)		−1.96 (0.901)		−1.49 (0.906)
95% CI		(−3.74, −0.18)		(−3.28, 0.30)
Effect size[d]		0.27		
HAM-A response at Week 8				
Baseline *n* value			148	149
Subjects with response				
n (response rate) (linear regression on LOCF)[c]			59 (39.9%)	92 (61.7%)

Table 2 (*continued*)

Key secondary variables				
P value				<0.001
LS mean difference from placebo (SE)				2.393
95% CI				(1.496, 3.830)
HAM-A total score for subjects with baseline HAM-A ≥25				
Baseline *n* value	100	96	100	96
Baseline LS mean (SE)	28.20 (0.315)	28.31 (0.322)	28.20 (0.315)	28.31 (0.322)
Change from baseline to Week 8				
n				
LS mean (SE)	82	82	100	96
P value	−10.44 (0.895)	−15.55 (0.904) <0.001	−9.34 (0.891)	−14.86 (0.910) <0.001-3.84
LS mean difference from placebo (SE)				
95% CI		−5.10 (1.267); (−7.61, −2.60)		−0.973 (−5.75, −1.92)
Effect size[d]		0.71		
SF-36 social functioning subscore				
Baseline *n* value	147	149	147	149
Baseline LS mean (SE)	44.16 (1.948)[c]	44.19 (1.925)c	44.16 (1.948)[c]	44.19 (1.925)[c]
Change from baseline to Week 8				
n	128	129	147	149
LS mean (SE)	18.02 (1.991)	26.80 (1.974)	16.67 (1.966)	24.78 (1.943)
P value		0.002		0.003
LS mean difference from placebo (SE)		8.78 (2.774)		8.11 (2.703)
95% CI		(3.32, 14.25)		(2.79, 13.43)
Effect size[d]		0.38		

Abbreviations: FAS, full analysis set; MMRM, mixed model for repeated measurements; ANCOVA, analysis of covariance; LOCF, last observation carried forward; CI, confidence interval.

[a]"*n*" refers to the number of subjects based on observed case (OC) data. Calculated on the LS mean change from baseline at Week 8, by MMRM on OC data.

[b]CGI-S score used as a baseline value.

[c]Response was defined as a decrease from baseline of ≥50% in the HAM-A total score.

[d]Effect size was calculated based on observed cases.

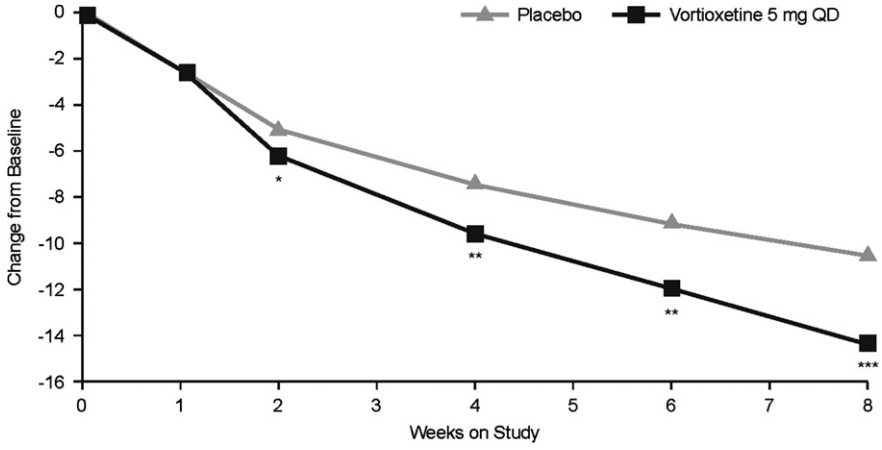

Figure 2 HAM-A total score: least-squaures mean change from baseline assessed at each visit (MMRM on FAS). *$P<0.05$, **$P<0.01$ and ***$P<0.001$.

baseline ±SE in HAM-A total score at Week 8 was −14.3±0.7 for the vortioxetine group and −10.5±0.7 for the placebo group (difference, −3.81±0.981; 95% CI, −5.74, −1.88 MMRM; $P<0.001$). The effect size for the primary endpoint analysis was 0.55. These positive efficacy results were replicated by the ANCOVA analyses using both

LOCF and OC data sets (Table 2). The mean HAM-A total score for the vortioxetine group separated from that of the placebo group from Week 2 onward, with a nominal $P<0.05$ (Figure 2).

3.3. Secondary efficacy outcomes

Subjects who received vortioxetine had statistically significant improvement (vs placebo) from baseline to Week 8 in all six key secondary efficacy endpoints ($P<0.05$), based on the prespecified sequential testing procedure (Table 2). Results were replicated using the ANCOVA model on both LOCF and OC data for five of the key secondary efficacy endpoints. However, for SDS total score, the change from baseline to Week 8 did not separate from placebo (ANCOVA LOCF, nominal $P=0.102$; ANCOVA OC, $P=0.065$).

The percentage of subjects who achieved a response by Week 8 in the vortioxetine group was higher than in the placebo group (odds ratio (OR), 2.393 (95% CI, 1.496, 3.830; nominal $P<0.001$). The response rate at Week 8 was 62% in the vortioxetine group and 40% in the placebo group, corresponding to an NNT of 5.

Subjects in the vortioxetine group also were more likely to have achieved remission (defined as a HAM-A total score ≤ 7) by Week 8 (OR, 1.958; 95% CI, 1.106–3.465; nominal $P=0.021$). Remission rates were 30% for the vortioxetine group and 18% for the placebo group, corresponding to an NNT of 9.

The LS mean change from baseline at Week 8 (MMRM) showed greater improvement (nominal $P<0.05$) with vortioxetine for 13 of the 14 HAM-A individual items (data not shown). The exception was Item 11, gastrointestinal symptoms (nominal $P=0.097$).

3.4. Subgroup analyses

Changes from baseline to Week 8 in HAM-A total scores were analyzed by age (≤ 55 years and >55 years), gender, and baseline severity of GAD (HAM-A total score <25 and ≥ 25) (Table 3). Improvement in the primary endpoint was significantly greater in the vortioxetine group relative to the placebo group for all subgroups except those >55 years of

Table 3 Subgroup analysis for the primary endpoint (MMRM).

Variable	Study group	
	Placebo ($n=151$)	Vortioxetine 5 mg ($n=150$)
Age		
Age ≤ 55 years[a]		
Change from baseline at Week 8, *n*	92	94
LS mean (SE)	−10.26 (0.793)	−15.51 (0.793)
P value (active vs placebo)		<0.001
Age >55 years[a]		
Change from baseline at Week 8, *n*	34	34
LS mean (SE)	−11.06 (1.399)	−10.44 (1.419)
P value (active vs placebo)		0.756
Gender		
Male		
Change from baseline at Week 8, *n*	50	40
LS mean (SE)	−8.92 (1.203)	−12.94 (1.316)
P value (active vs placebo)		0.026
Female		
Change from baseline at Week 8, *n*	76	88
LS mean (SE)	−11.49 (0.874)	−14.79 (0.829)
P value (active vs placebo)		0.007
HAM-A total score at baseline		
Score <25		
Change from baseline at Week 8, n	44	46
LS mean (SE)	−10.98 (1.192)	−12.05 (1.140)
P value (active vs placebo)		0.511
Score ≥ 25		
Change from baseline at Week 8, *n*	82	82
LS mean (SE)	−10.44 (0.895)	−15.55 (0.904)
P value (active vs placebo)		<0.001

Note: Only results from the primary analysis are provided (MMRM on OC data).

[a]Data for age ≤ 65 years and >65 years are not included because $<20\%$ of subjects were >65 years of age.

Table 4 Treatment-emergent adverse events (TEAEs) reported for ≥5% of subjects in at least one study group (safety population).

SOC term/preferred term	Study group			
	Placebo (n=150)		Vortioxetine 5 mg (n=150)	
	Events	Subjects (%)	Events	Subjects (%)
Any TEAE[a]	106	55 (36.7)	137	74 (49.3)
Gastrointestinal disorders				
Nausea	10	9 (6.0)	19	18 (12.0)
Nervous system disorders				
Headache	14	13 (8.7)	18	12 (8.0)
Dizziness	5	4 (2.7)	10	9 (6.0)

Abbreviation: SOC, system order class (SOC).
[a]Defined as any adverse event with onset occurring, or intensity increasing, after the first dose of study medication until 30 day after discontinuation of study medication.

age (n=78, 25.9% of the FAS) and those with baseline HAM-A total score <25.

A post hoc analysis was performed to assess change from baseline in HAM-A total scores in subjects who had previously received medication for GAD and those who were treatment-naïve. Numeric differences favoring vortioxetine were seen in both subgroups. For those who had been treated previously, the mean change from baseline in HAM-A total score for vortioxetine did not separate from that of placebo (difference in mean change, −2.21; P=0.152). However among-treatment naïve subjects, those in the vortioxetine group showed greater improvement than those in the placebo group (difference in mean change, −5.19; P<0.001).

3.5. Safety and tolerability endpoints

The most frequently reported treatment-emergent AEs (TEAEs), occurring in ≥5% of subjects in at least one study group (safety population), were nausea, headache, and dizziness as shown in Table 4. In the vortioxetine group, the rates of AEs considered related to study treatment were 11.3% for nausea, 6.7% for headache, and 5.3% for dizziness. The placebo rates were 3.3% for nausea, 6.0% for headache, and 2.7% for dizziness. Dry mouth occurred in 3.3% of the vortioxetine group and 2.7% of the placebo group. The incidence of sexual side effects was <1%. One serious AE (intervertebral disc protrusion) occurred in a placebo subject and was considered unrelated to study medication. There were no deaths in either group. Of the 47 (15.6%) subjects (including the one who was randomized but not treated) who discontinued study treatment early, 16 (7 on placebo; 9 on vortioxetine) discontinued because of AEs. Most AEs, including those resulting in discontinuation, were of mild to moderate severity.

No clinically important trends in physical findings, weight, or vital signs were observed between the study groups, nor were there any clinically significant differences in laboratory or ECG findings. There were no clinically meaningful differences between the study groups in suicidal ideation or behavior, as assessed by the C-SSRS.

4. Discussion

Vortioxetine provided significant improvement in the primary endpoint (change from baseline in HAM-A total score) in a multinational population with GAD, as demonstrated by the primary analysis and confirmed by sensitivity analyses using ANCOVA with LOCF and OC data sets. Separation from placebo was observed starting at Week 2. In addition, vortioxetine showed significant benefits (vs placebo) in all six key secondary endpoints in the prespecified hierarchy. These included change from baseline at Week 8 in HAD anxiety subscore, CGI-I, SDS total score, HAM-A response rate, HAM-A total score in patients with baseline HAM-A total score ≥25, and SF-36 social functioning subscore. All secondary endpoints reached statistical significance using ANCOVA LOCF except the SDS total score (P=0.102). The failure to reach statistical significance may be a function of the much smaller sample size of the SDS total score data set (Table 2) in comparison to the sample sizes for other outcome measures. These results show consistent benefit of vortioxetine across a range of clinical and functional measures. Moreover, improvement was reported by clinicians (HAM-A, CGI-I and CGI-S) as well as subjects (HAD, SDS, SF-36). These findings are consistent with results in clinical trials of antidepressants approved for the treatment of GAD (Davidson, et al., 1999, 2004; Rynn et al., 2008; Pollack et al., 2001; Brawman-Mintzer et al., 2006; Baldwin et al., 2006; Allgulander et al., 2001, 2004; Koponen et al., 2007; Hartford et al., 2007).

Analyses of the primary efficacy endpoint were conducted for the following prespecified variables: age (≤55 vs >55 years), gender, and baseline severity of GAD (HAM-A total score <25 and ≥25). Patients with more severe GAD had a significantly greater benefit from treatment with vortioxetine relative to placebo. Significant improvement was observed for men and women. Patients ≤55 years of

age showed significant improvement with vortioxetine (vs placebo), but those over 55 years of age did not. The absence of a significant effect in the older patients may reflect the small sample size; only 78 (34 per study group) subjects (~26%) were older than 55. An analysis of clinical trials in patients with MDD (Khin et al., 2011) showed that a higher risk of placebo effect in trials with mean baseline HAM-D scores <20 was associated with a lower likelihood of observing a statistically significant benefit with active treatment. It is reasonable to hypothesize that, in the current study, a similar effect may account for the non-significant difference between active treatment and placebo among subjects whose baseline HAM-A total score was <25.

Although the results of this study consistently favor treatment with vortioxetine, significant improvement was not observed in any efficacy endpoint of the companion study conducted in the US (Rothschild et al., in preparation). The obvious difference between the two studies of identical design is the geographic region in which they were conducted. The current study was performed entirely outside the US, whereas the companion study was conducted solely within the US. The possible reasons for the differential outcomes are discussed at length in the accompanying article (Rothschild et al., in preparation).

In the current study, 42% of subjects had received antidepressant therapy for GAD before enrollment. Only 22% of subjects in the US study had previous experience with drug therapy for GAD. To investigate a potential effect of previous drug therapy on clinical outcomes, we conducted a post hoc analysis of the primary endpoint in subjects who were treatment-naive and in those with prior exposure to drug therapy. Compared with placebo, treatment-naïve subjects showed greater improvement in HAM-A total score with vortioxetine compared with placebo. In contrast, the primary endpoint was statistically similar between treatments in the subgroup with prior drug therapy. Based on these findings, it is unlikely that the difference in prior drug experience explains the difference in clinical outcomes between the trials. The potential clinical relevance of this observation requires further investigation. The results of this and other post hoc analyses of differences between the US and non-US trials warrant consideration beyond the primary manuscript and are being considered for a subsequent publication.

The current multinational study has several limitations. First, an active control was not included in the study design. Second, the study population may not be representative of all people who seek treatment for GAD. For example, the entire population recruited was Caucasian; US subjects were not included; and individuals with comorbid psychiatric/medical diagnoses, concurrent treatments, or substance abuse were excluded. In addition, samples were not collected for pharmacokinetic analysis to evaluate whether the unexpectedly low rate of AEs could be explained by low drug exposure or nonadherence to treatment.

In conclusion, vortioxetine provided consistent benefit across a range of endpoints in this large non-US population with a primary diagnosis of GAD. The results demonstrate statistical significance when analyzed using MMRM, ANOVA, LOCF, and OC. Vortioxetine was safe and well tolerated, as it was in the companion study (Rothschild et al., in preparation), and in three trials that investigated vortioxetine for the treatment of MDD (Alvarez et al., 2011; Henigsberg et al., 2011; Baldwin et al., 2011b). The results of the current study suggest that vortioxetine may be an effective treatment for primary GAD.

Role of funding source

This study was sponsored by the Takeda Pharmaceutical Company, Ltd., as part of a joint clinical development program with H. Lundbeck A/S. Assistance with writing and manuscript preparation was provided by The Medicine Group. This study was funded by the Takeda Pharmaceutical Company, Ltd. The authors were involved in the study design, analysis and interpretation of data, writing the report and decision to submit for publication.

Contributors

Author Leszek Bidzan participated in reviewing the study results, and in reviewing and revising the manuscript.

Author Atul R. Mahableshwarkar was involved in providing medical oversight to the study; data cleaning and interpretation; and planning, writing, reviewing, and revising the manuscript.

Author Paula Jacobsen was involved in protocol development; study oversight; data cleaning and interpretation; and planning, writing, reviewing, and revising the manuscript.

Author Mingjin Yan was involved in protocol development; study oversight; planning and conducting statistical analyses; data cleaning and interpretation; and reviewing and revising the manuscript.

Author David V. Sheehan participated in planning, reviewing, and revising the manuscript.

Conflict of interest

In the past 3 years, Dr. Leszek Bidzan has received research grants from Eli Lilly and has given industry-sponsored lectures for Eli Lilly, Janssen Cilag, Lundbeck, Novartis, Pfizer, KRKA, and Sanofi Aventis.

Drs. Mahableshwarkar, Jacobsen, and Yan are employees of Takeda Global Research & Development Inc.

In the past 3 years, Dr. David Sheehan has received grant support, or has been affiliated with or received honoraria and travel expenses related to lectures/presentations or consultant activities, from the following companies and organizations: Abbott Laboratories, Ad Hoc Committee, Treatment Drug & Assessment Research Review, Alexa, Alza Pharmaceuticals, American Medical Association, American Psychiatric Association Task Force on Benzodiazepine Dependency, American Psychiatric Association Task Force on Treatments of Psychiatric Disorders, American Psychiatric Association Working Group to revise DSM III Anxiety Disorders Section, Anclote Foundation, Anxiety Disorders Resource Center, Anxiety Drug Efficacy Case, US Food & Drug Administration, Applied Health Outcomes/Xcenda, AstraZeneca, Avera Pharmaceuticals, Boehringer Ingelheim, Boots Pharmaceuticals, Bristol-Myers Squibb, Burroughs Wellcome, Cephalon, Charter Hospitals, Ciba Geigy, Committee (RRC) of NIMH on Anxiety and Phobic Disorder Projects, Connecticut & Ohio Academies of Family Physicians, Cortex Pharmaceutical, Council on Anxiety Disorders, CPC Coliseum Medical Center, Cypress Bioscience, Dista Products Company, Division of Drugs & Technology, American Medical Association, EISAI, Eli Lilly, Excerpta Medica Asia, Faxmed, Inc1, Forest Laboratories, Glaxo Pharmaceuticals, GlaxoSmithKline, Glaxo-Wellcome, Hikma Pharmaceuticals, Hospital Corporation of America, Humana, ICI, INC Research, International Clinical Research (ICR), International Society for CNS Drug Development (ISCDD), Janssen Pharmaceutica, Jazz Pharmaceuticals, Kali-Duphar, Labopharm-Angellini, Layton Bioscience, Lilly Research Laboratories, Lundbeck (Denmark),

Marion Merrill Dow, McNeil Pharmaceuticals, Mead Johnson, Medical Outcome Systems, MediciNova, Merck Sharp & Dohme, National Anxiety Awareness Program, National Anxiety Foundation, National Depressive & Manic Depressive Association, National Institute of Drug Abuse, National Institute of Health (NIH), Neuronetics, Nova-Del, Novartis Pharmaceuticals, Novo Nordisk, Organon, Orion Pharma, Parexel International Corporation, Parke-Davis, Pfizer, Pharmacia, Pharmacia & Upjohn, PharmaNeuroBoost, Philadelphia College of Pharmacy & Science, Pierre Fabre (France), Quintiles, Rhone Laboratories, Rhone-Poulenc Rorer Pharmaceuticals, Roche, Roerig, Sagene, Sandoz Pharmaceuticals, Sanofi-Aventis, Sanofi-Synthelabo Recherche, Schering Corporation, Sepracor, Shire Laboratories, SmithKlineBeecham, Solvay Pharmaceuticals, Takeda, Tampa General Hospital, University of South Florida Psychiatry Center, University of South Florida College of Medicine, TAP Pharmaceuticals, Targacept, TGH-University Psychiatry Center, Tikvah Therapeutics, Titan Pharmaceuticals, United Bioscience, The Upjohn Company, US Congress-House of Representatives Committee, USF Friends of Research in Psychiatry (Board of Trustees), Warner Chilcott, World Health Organization, Worldwide Clinical Trials, Wyeth-Ayerst, ZARS, Zeneca Pharmaceuticals, Neuronetics.

Acknowledgments

This study was sponsored by the Takeda Pharmaceutical Company, Ltd., as part of a joint clinical development program with H. Lundbeck A/S. Assistance with writing and manuscript preparation was provided by Ann Sherwood, PhD, of The Medicine Group, and funded by the Takeda Pharmaceutical Company, Ltd.

References

Allgulander, C., Hackett, D., Salinas, E., 2001. Venlafaxine extended release (ER) in the treatment of generalised anxiety disorder: twenty-four-week placebo-controlled dose-ranging study. Br. J. Psychiatry 179, 15–22.

Allgulander, C., Dahl, A.A., Austin, C., Morris, P.L., Sogaard, J.A., Fayyad, R., Kutcher, S.P., Clary, C.M., 2004. Efficacy of sertraline in a 12-week trial for generalized anxiety disorder. Am. J. Psychiatry 161 (9), 1642–1649.

Alvarez, E., Perez, V., Dragheim, M., Loft, H., Artigas, F., 2011. A double-blind, randomized, placebo-controlled, active reference study of Lu AA21004 in subjects with major depressive disorder. Int. J. Neuropsychopharmacol., pp. 1–12. http://dx.doi.org/10.1017/S1461145711001027 (Epub ahead of print).

American Psychiatric Association, 2000. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), fourth ed. American Psychiatric Association, Washington, DC.

Baldwin, D.S., Waldman, S., Allgulander, C., 2011a. Evidence-based pharmacological treatment of generalized anxiety disorder. Int. J. Neuropsychopharmacol. 14 (5), 697–710.

Baldwin, D.S., Loft, H., Dragheim, M., 2011b. A randomised, double-blind, placebo controlled, duloxetine-referenced, fixed-dose study of three dosages of Lu AA21004 in acute treatment of major depressive disorder (MDD). Eur. Neuropsychopharmacol.http://dx.doi.org/10.1016/j.euroneuro.2011.11.008 (Epub ahead of print).

Baldwin, D.S., Huusom, A.K., Maehlum, E., 2006. Escitalopram and paroxetine in the treatment of generalised anxiety disorder: randomised, placebo-controlled, double-blind study. Br. J. Psychiatry 189, 264–272.

Bang-Andersen, B., Ruhland, T., Jorgensen, M., Smith, G., Frederiksen, K., Jensen, K.G., 2011. Discovery of 1-[2-(2,4-dimethylphenylsulfanyl)phenyl]piperazine (Lu AA21004): a novel multimodal compound for the treatment of major depressive disorder. J. Med. Chem. 54 (9), 3206–3221.

Bobes, J., Caballero, L., Vilardaga, I., Rejas, J., 2011. Disability and health-related quality of life in outpatients with generalised anxiety disorder treated in psychiatric clinics: is there still room for improvement? Ann. Gen. Psychiatry 10 (1), 7.

Brawman-Mintzer, O., Knapp, R.G., Rynn, M., Carter, R.E., Rickels, K., 2006. Sertraline treatment for generalized anxiety disorder: a randomized, double-blind, placebo-controlled study. J. Clin. Psychiatry 67 (6), 874–881.

Davidson, J.R., Bose, A., Korotzer, A., Zheng, H., 2004. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. Depression Anxiety 19 (4), 234–240.

Davidson, J.R., DuPont, R.L., Hedges, D., Haskins, J.T., 1999. Efficacy, safety, and tolerability of venlafaxine extended release and buspirone in outpatients with generalized anxiety disorder. J. Clin. Psychiatry 60 (8), 528–535.

Guy, W., 1976. The clinical global impression severity and impression scales. In: EDEU Assessment Manual for Psychopathology. US Department of Health, Education and Welfare, Rockville, MD, pp. 2118–2122.

Hamilton, M., 1959. The assessment of anxiety states by rating. Br. J. Med. Psychol. 32 (1), 50–55.

Hartford, J., Kornstein, S., Liebowitz, M., Pigott, T., Russell, J., Detke, M., Walker, D., Ball, S., Dunayevich, E., Dinkel, J., Erickson, J., 2007. Duloxetine as an SNRI treatment for generalized anxiety disorder: results from a placebo and active-controlled trial. Int. Clin. Psychopharmacol. 22 (3), 167–174.

Henigsberg, N., Mahableshwarkar, A.R., Jacobsen, P., Chen, Y., Thase, M.E., 2011. Efficacy and safety of multiple doses of Lu AA21004 in an 8-week treatment of adults with major depressive disorder. Eur. Neuropsychopharmacol. 21 (Suppl. 3), S393.

Hoffman, D.L., Dukes, E.M., Wittchen, H.-U., 2008. Human and economic burden of general anxiety disorder. Depression Anxiety 25 (1), 72–90.

Jain, R., Mahableshwarkar, A.R., Jacobsen, P., Chen, Y., Thase, M.E. Efficacy and safety of 6 weeks treatment with Lu AA21004 5 mg in adults with major depressive disorder. Int. J. Neuropsychopharmacol., submitted for publication.

Kessler, R.C., Chiu, W.T., Demler, O., Walters, E.E., 2005. Prevalence, severity, and comorbidity of twelve-month DSM-IV disorders in the National Comorbidity Survey Replication (NCS-R). Arch. Gen. Psychiatry 62 (6), 617–627.

Khin, N.A., Chen, Y.-F., Yang, Y., Yang, P., Laughren, T.P., 2011. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. J. Clin. Psychiatry 72, 464–472.

Koponen, H., Allgulander, C., Erickson, J., Dunayevich, E., Pritchett, Y., Detke, M.J., Ball, S.G., Russell, J.M., 2007. Efficacy of duloxetine for the treatment of generalized anxiety disorder: implications for primary care physicians. Prim. Care Companion J. Clin. Psychiatry 9 (2), 100–107.

Leon, A.C., Olfson, M., Portera, L., Farber, L., Sheehan, D.V., 1997. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. Int. J. Psychiatry Med. 27 (2), 93–105.

Montgomery, S.A., Åsberg, M., 1979. A new depression scale designed to be sensitive to change. Br. J. Psychiatry 134, 382–389.

Mørk, A., Pehrson, A., Tottrup Brennum, L., Moller Nielsen, S., Zhong, H., Lassen, A.B., Miller, S., Westrich, L., Boyle, N.J., Sanchez, C., Weide Fischer, C., Liebenberg, N., Wegener, G., Bundgaard, C., Hogg, S., Bang-Andersen, B., Bryan Stensbol, T.J., 2011. Pharmacol. Exp. Ther. (Epub ahead of print).

Pollack, M.H., Zaninelli, R., Goddard, A., McCafferty, J.P., Bellew, K.M., Burnham, D.B., Iyengar, M.K., 2001. Paroxetine in the treatment of generalized anxiety disorder: results of a placebo-controlled, flexible-dosage trial. J. Clin. Psychiatry 62 (5), 350–357.

Posner, K., Oquendo, M.A., Gould, M., Stanley, B., Davies, M., 2007. Columbia classification algorithm of suicide assessment (C-CASA): classification of suicidal events in the FDA's pediatric suicidal risk analysis of antidepressants. Am. J. Psychiatry 164 (7), 1035–1043.

Rothschild, A., Mahableshwarkar, A., Jacobsen, P., Yan, M., Sheehan, D. Lu AA21004 in generalized anxiety disorder: results of an 8-week randomized, double-blind clinical trial in the US, in preparation.

Rynn, M., Russell, J., Erickson, J., Detke, M.J., Ball, S., Dinkel, J., Rickels, K., Raskin, J., 2008. Efficacy and safety of duloxetine in the treatment of generalized anxiety disorder: a flexible-dose, progressive-titration, placebo-controlled trial. Depression Anxiety 25 (3), 182–189.

Sheehan, D.V., Lecrubier, Y., Harnett-Sheehan, K., Amorim, P., Janavs, J., Weiller, E., Hergueta, T., Baker, R., Dunbar, G., 1998. The Mini International Neuropsychiatric Interview (MINI): the development and validation of a structured diagnostic psychiatric interview. J. Clin. Psychiatry 59 (Suppl. 20), 22–33.

Ware Jr., J.E., Sherbourne, C.D., 1992. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med. Care 30 (6), 473–483.

Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., et al., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol. 21 (9), 655–679.

Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. Acta Psych. Scand. 67 (6), 361–370.