Evaluation of the Glycine Transporter Inhibitor Org 25935 as Augmentation to Cognitive-Behavioral Therapy for Panic Disorder: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial

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ABSTRACT

Objective: A growing body of evidence supports the efficacy of D-cycloserine (DCS), a partial agonist at the *N*-methyl-D-aspartate (NMDA) glutamate receptor, as augmentation to cognitive-behavioral therapy (CBT) in the treatment of anxiety disorders. Org 25935 is a glycine transporter 1 inhibitor that acts to increase synaptic glycine levels and enhance NMDA-mediated glutamatergic activity. The aim of this study was to examine the efficacy of a glutamatergic compound other than DCS in a CBT augmentation paradigm.

Method: This was a randomized, double-blind, placebo-controlled, parallel-group clinical trial for which participants were recruited from November 2008 through February 2010. Eligible adult patients diagnosed (*DSM-IV*) with panic disorder with or without agoraphobia (N = 40) were scheduled to receive 5 manualized CBT treatment sessions. Participants were randomly assigned to receive either a dose of Org 25935 (4 mg or 12 mg) or placebo 2 hours prior to the start of CBT sessions 3, 4, and 5. The primary endpoint was symptomatic change as measured by the Panic Disorder Severity Scale (PDSS) 1 week following the last CBT session.

Results: Although mean PDSS total scores decreased significantly from baseline to end of treatment in every group, no statistically significant benefit was observed for Org 25935 (4 or 12 mg) over placebo on the primary endpoint or on any secondary efficacy endpoint. Org 25935 showed no safety issues at either dose but was much better tolerated at the 4-mg dose level than at the 12-mg dose level.

Conclusions: Org 25935 demonstrated no benefit over placebo in augmenting CBT for panic disorder. Study limitations and implications are discussed.

Trial Registration: clinicaltrials.gov Identifier: NCT00725725

J Clin Psychiatry 2012;73(5):647–653

Submitted: *April 19, 2011; accepted July 11, 2011.*
Online ahead of print: *February 21, 2012 (doi:10.4088/JCP.11m07081).*
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Although efficacious, cognitive-behavioral therapy (CBT) for anxiety disorders leaves ample room for improvement.[1] Animal research of fear extinction, a central mechanism underlying the effects of CBT,[2,3] points to promising targets for optimizing outcomes with CBT.[4] One such target is the glutamate system, and particularly the *N*-methyl-D-aspartate (NMDA) receptors,[5] which plays an essential role in memory and learning via synaptic plasticity and long-term potentiation.[6,7] Prompted by investigations implicating a critical role for NMDA receptors in extinction learning,[8] a series of studies demonstrated that D-cycloserine (DCS), a partial NMDA agonist, facilitates extinction consolidation in rodents.[9]

In human trials, an initial positive finding for DCS augmentation of exposure interventions in height phobia[10] was later followed by positive effects in similar small- and medium-scale placebo-controlled trials for panic disorder,[11] social anxiety disorder,[12,13] and obsessive-compulsive disorder.[14–16] With few exceptions, these trials have yielded DCS effects that are clinically meaningful (effect size $d = 0.60$).[17] Importantly, beneficial effects of DCS have been observed when it is administered in isolated doses (eg, only in conjunction with CBT sessions); chronic dosing, on the other hand, may have neutral or detrimental effects on learning, possibly due to receptor desensitization.[18]

In the recent study by Otto and colleagues,[11] 31 outpatients with panic disorder with or without agoraphobia received DCS or placebo 1 hour prior to 3 of 5 CBT sessions, during which interoceptive exposure exercises (ie, repeated induction of somatic symptoms associated with anxiety) were conducted. The group receiving DCS augmentation showed significantly greater reduction on the primary outcome measure (Panic Disorder Severity Scale; PDSS)[19] than did the placebo group, resulting in a large effect size at posttreatment ($d = 1.11$) as well as a maintenance of the DCS advantage at 1 month posttreatment.

It is proposed that similar effects on extinction learning may be achieved by increasing synaptic glycine levels. Glycine acts as an obligatory coagonist for activation of the NMDA-gated voltage-dependent cation channel through action at strychnine-insensitive glycine sites (Gly-B).[20] The glycine transporter-1 (GlyT1) plays a pivotal role in maintaining the concentration of glycine within synapses at a subsaturation level.[21–23] Increasing the synaptic concentration of glycine through attenuation of its reuptake may thus enhance glutamatergic NMDA receptor–mediated neurotransmission in a non-excitotoxic fashion.[24,25] Further, the beneficial effects of glycine uptake inhibition on cognition are well supported by animal work.[26–29]

Org 25935 (chemical name: *N*-methyl-*N*-[[(1R,2S)-1,2,3,4-tetrahydro-6-methoxy-1-phenyl-2-naphthalenyl]methyl]-glycine hydrochloride) acts as a glycine uptake inhibitor, demonstrating moderate potency and

high selectivity for the GlyT1 transporter in vitro[30] and raises extracellular glycine levels in rodents.[31,32]

Animal work with Org 25935 provides supportive evidence for its ability to potentiate NMDA activity (all data on file). In vitro and in vivo electrophysiological experiments show that Org 25935 increases NMDA, responding in a dose-dependent fashion. Further, NMDA receptor activation in the presence of Org 25935 results in a potentiation of taurine release in the rat striatum. Locomotor activity is significantly increased by Org 25935, and this activity is blocked by coadministration with the NMDA antagonist MK801. Finally, Org 25935, at lower but not higher doses, reverses PCP-induced deficits in rat novel object recognition, a model suggestive of benefits on working memory.

In the current trial, we examined the efficacy of Org 25935 (4 mg and 12 mg) in the context of the Otto et al study design and treatment paradigm.[11] Previous work in healthy human volunteers (data on file) showed that mean glycine concentrations in cerebrospinal fluid (CSF) were increased approximately 2.5 fold after a single oral dose of 16 mg, whereas a smaller increase (approximately 1.5 fold) was found after a 4-mg dose, thereby providing evidence for target engagement in the aforementioned dose range. Glycine T_{max} was approximately 4 hours postdose (data on file). Higher doses were not considered for the current trial, given the history of subjective visual adverse events associated with Org 25935 (data on file). The primary hypothesis was that CBT augmentation with Org 25935 would result in better treatment outcomes than augmentation with placebo, as measured by the PDSS at posttreatment.

METHOD

Participants

Participants were recruited at 4 academic research centers from November 2008 through February 2010. This trial was conducted in accordance with the principles of Good Clinical Practice and was approved by each center's institutional review board prior to commencement of study activities. All study participants signed an informed consent form before any screening evaluations were performed. The trial was registered at clinicaltrials.gov (Identifier: NCT00725725).

Study participants were 18 to 65 years of age, of either sex or any race, and were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*)[33] at screening with panic disorder, with or without agoraphobia. Eligible patients had a Clinical Global Impressions–Severity of Illness (CGI-S) scale[34] score of 4 to 6 (moderately ill to severely ill) and permitted concurrent psychotropic medication included only antidepressants and anxiolytics that had been stabilized for at least 8 weeks prior to screening. Patients were excluded from the trial if they had any lifetime history of psychotic disorder, bipolar disorder, or obsessive-compulsive disorder; a 6-month history of posttraumatic stress disorder, eating disorder, or substance abuse; recent suicidality; or current severe depression (Montgomery-Asberg Depression Rating Scale score ≥ 35).[35] Patients were also excluded if there was any reported or discovered unstable, clinically significant medical condition. Female participants were required to use an acceptable method of contraception during the trial. Baseline participant characteristics are presented in Table 1.

Table 1. Participant and Illness Characteristics at Baseline, All-Subjects-Treated Population

	Org 25935 4 mg (n = 11)	Org 25935 12 mg (n = 15)	Placebo (n = 14)
Age, mean (SD), y	33.3 (11.0)	36.4 (8.9)	32.4 (11.2)
Female, n (%)	7 (63.6)	9 (60.0)	11 (78.6)
White, n (%)	9 (81.8)	14 (93.3)	13 (92.9)
Panic disorder with agoraphobia, n (%)	10 (90.9)	13 (86.7)	12 (85.7)
Panic disorder without agoraphobia, n (%)	1 (9.1)	2 (13.3)	2 (14.3)
Current comorbid anxiety disorder, n (%)	3 (27.3)	7 (46.7)	6 (42.9)
Current comorbid depressive disorder, n (%)	2 (18.2)	2 (13.3)	2 (14.3)
Concurrent stabilized SSRI or other antidepressant, n (%)	2 (18.2)	3 (20.0)	4 (28.6)
Concurrent stabilized benzodiazepine, n (%)	2 (18.2)	4 (26.7)	4 (28.6)

Procedures

Screening procedures included psychiatric interview by the principal investigator or a similarly qualified designee (all licensed clinical psychologists) and confirmation of primary and comorbid diagnoses using the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Patient Edition With Psychotic Screen.[36] In addition, patients were assessed for symptom severity using all efficacy measures. Screening safety assessments included medical history, physical examination, electrocardiogram, vital signs, routine clinical laboratory testing, and an ophthalmology exam to rule out clinically relevant preexisting visual conditions.

Eligible patients were randomized via an interactive voice response system to receive CBT + Org 25935 (4 or 12 mg) or CBT + placebo in a 1:1:1 ratio. Patients returned to the clinic postrandomization for 5 weekly treatment visits, an end-of-treatment visit 1 week following the last CBT session (end of treatment), and a follow-up treatment visit 1 month following the last CBT session (follow-up). CBT was delivered in 60- to 90-minute individual treatment sessions, with sessions 3 to 5 focused on interoceptive exposure exercises tailored to the needs of the patient. Participants received a double-blinded dose of Org 25935 or placebo 2 hours prior to the start of CBT sessions 3, 4, and 5, the timing of which was planned so that CSF glycine T_{max} would correspond to the learning and memory consolidation period following the CBT session.[37] Patients received a total of 3 doses of study medication, and compliance was 100%, ie, every subject who did not discontinue prior to CBT sessions 3, 4, and/or 5 received the planned dose prior to those sessions. Org 25935 and matching placebo were prepared as white tablets for oral administration.

Assessment

The primary outcome measure was the PDSS, a 7-item clinician-rated instrument that assesses multiple dimensions of panic disorder severity.[19,38] Secondary outcome measures included the single-item CGI-S,[34] clinician-rated measures of general anxiety (Hamilton Anxiety Rating Scale–Structured Interview Version; SIGH-A)[39,40] and depression (MADRS),[35] as well as psychometrically sound self-report scales of anxiety sensitivity (Anxiety Sensitivity Index; ASI)[41] and quality of life (Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form; Q-LES-Q-SF).[42]

Efficacy scales were administered at screening (the efficacy baseline), end of treatment, and follow-up. In addition, the PDSS was administered at week 4, and the CGI was performed weekly. Postrandomization safety and tolerability were assessed via open-ended questioning for adverse events (every visit), vital signs (every visit through end of treatment), electrocardiogram (after the first dose of study medication and at end of treatment), routine clinical laboratory examinations (week 4 and end of treatment), physical and ophthalmologic examination (end of treatment), and the Columbia Suicide Severity Rating Scale (every visit).

Experienced CBT therapists participated in pretrial group training on the study-specific treatment approach, followed by regular supervision conducted by the local and lead investigators. Treatment was conducted following the protocol employed by Otto and colleagues,[11] and treatment adherence and competence were established through independent review of session audio recordings. Efficacy ratings were performed by trained and experienced raters who did not also serve as the therapist for any given study patient. All study raters were qualified through calibration exercises prior to rating in the trial.

Analytic Plan

A sample size of 20 patients per group was planned in order to yield at least 90% power to detect a treatment effect size of 0.97, assuming a within-subject repeated measures correlation of 0.8. Following the merger of Schering-Plough and Merck, and a review of ongoing development programs, a decision was taken to prematurely stop recruitment due to a combination of the difficulties completing enrollment and a decision not to pursue the indication under study. At that point, approximately 75% of planned participants had been randomized, yielding a power of 0.70–0.77 to detect group differences. Despite this, efficacy analyses were undertaken using the same analytic approach that had been established a priori.

All efficacy analyses were conducted using the intent-to-treat (ITT) population (patients who received at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment). Continuous outcome measures were analyzed with a mixed model repeated measures analysis of covariance, with baseline entered as covariate and drug group, visit, site, and drug group × visit included as fixed effects. Analysis of CGI-based rate of remission (defined as a CGI score of 1 [normal, not at all ill] or 2 [borderline mentally ill]) was performed using a Fisher exact test. Statistical testing for each of the Org 25935 groups versus placebo was performed 2-sided at the .05 significance level, without adjustment for multiplicity. Safety analysis was undertaken using summary and descriptive statistics for the all-subjects-treated (AST) population (all patients who received at least 1 dose of study medication).

RESULTS

Patient Characteristics

A total of 101 patients provided informed consent and were screened for the study. Of these, 55 were screen failures. The majority were excluded because they failed to meet diagnostic criteria for panic disorder (n = 29) or because they did not wish to participate (n = 16). A total of 46 patients entered the trial and were randomized, 33 of whom completed treatment (71.7%). A total of 40 patients received at least the first dose of study medication at week 3 of treatment, qualifying them for the AST population. The ITT population included 37 patients: 10 in the 4-mg Org 25935 group, 14 in the 12-mg Org 25935 group, and 13 in the placebo group (Figure 1).

Most patients in the AST population were female (68%) and white (90%) and were diagnosed with panic disorder with agoraphobia (88%) (see Table 1). There were proportionally more females and more patients taking selective serotonin reuptake inhibitors or other antidepressants in the placebo group, as well as fewer patients in the 4-mg group diagnosed with comorbid anxiety disorders or who were taking benzodiazepines. None of these baseline group differences were statistically significant. Baseline symptomatic severity was generally greater in the placebo group than in the active drug groups, although this difference was statistically significant only for the PDSS (4-mg Org 25935 less severe than placebo; $P < .001$).

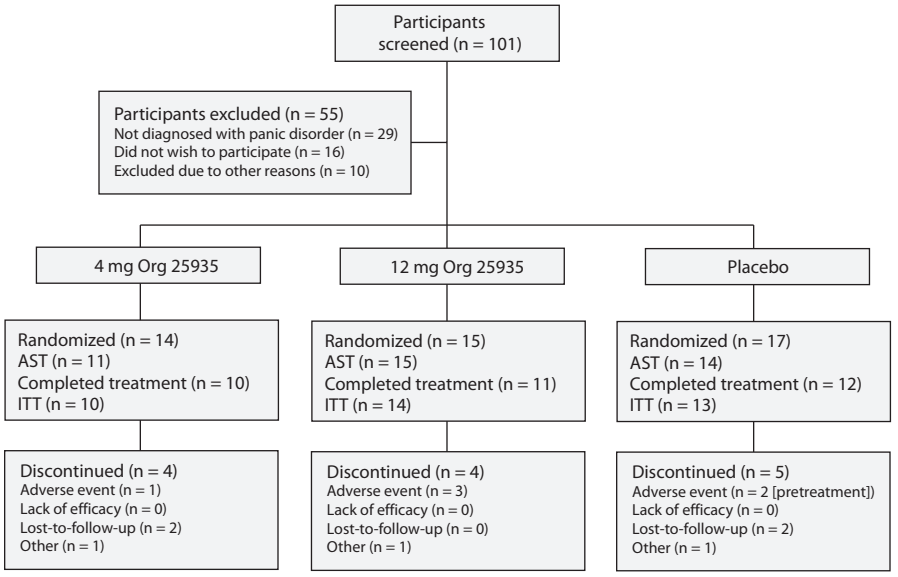
Primary Outcome Measure

Although mean PDSS total scores decreased from baseline to end of treatment in every group, reflecting significant symptomatic improvement (4-mg Org 25935: −6.2 ± 2.15; 12-mg Org 25935: −8.2 ± 4.49; placebo: −10.4 ± 4.23), there was no statistically significant difference between Org 25935 and placebo on change from baseline PDSS at end of treatment (4-mg Org 25935 versus placebo: $P = .39$; 12-mg Org 25935 versus placebo: $P = .35$) or at any other visit. At follow-up, the 12-mg Org 25935 versus placebo comparison was close to significant ($P = .08$) but favored placebo (Table 2 and Figure 2).

Secondary Outcome Measures

At end of treatment, CGI-based remission rates were 20% (2/10) in the 4-mg Org 25935 group, 29% (4/14) in the 12-mg Org 25935 group, and 33% (4/12) in the placebo group. At follow-up, remission rates were 40% (4/10) in the 4-mg Org 25935 group, 58% (7/12) in the 12-mg Org 25935 group, and 42% (5/12) in the placebo group. None of these differences was statistically significant. Similarly, analysis of all continuous efficacy measures yielded no significant findings, with

Figure 1. Progress of Participants in the Trial



Abbreviations: AST = All-Subjects-Treated Population, all patients who received at least 1 dose of study medication; ITT = Intent-to-Treat Population, patients who received at least 1 dose of study medication and had at least 1 postbaseline efficacy assessment.

Table 2. Means and Change From Baseline Confidence Intervals for Primary and Secondary Measures, Intent-To-Treat Population

	Mean (SD)			LS Mean Difference in Change From Baseline[a] (95% CI)	
Variable (score range)	Org 25935 4 mg (n = 10)	Org 25935 12 mg (n = 14)	Placebo (n = 13)	Org 25935 4 mg vs Placebo	Org 25935 12 mg vs Placebo
PDSS (0–28)					
Baseline	11.5 (1.51)	15.8 (4.00)	17.1 (3.99)	NA	NA
Week 4	7.1 (4.08)	10.5 (4.56)	12.2 (4.00)	−1.83 (−5.83 to 2.18)	−0.44 (−3.60 to 2.71)
End of treatment	5.3 (1.49)	7.6 (4.62)	6.6 (4.29)	1.53 (−2.08 to 5.14)	1.27 (−1.47 to 4.00)
Follow-up	4.8 (2.20)	7.4 (5.85)	5.3 (4.56)	2.34 (−1.89 to 6.56)	3.13 (−0.45 to 6.72)
SIGH-A (0–56)					
Baseline	17.2 (8.42)	14.3 (6.37)	14.6 (9.14)	NA	NA
End of treatment	9.7 (7.21)	10.0 (6.43)	8.5 (6.96)	0.35 (−4.62 to 5.31)	2.04 (−2.55 to 6.64)
Follow-up	8.0 (3.13)	9.7 (5.66)	9.4 (7.50)	−2.24 (−6.64 to 2.16)	1.02 (−3.75 to 5.78)
MADRS (0–60)					
Baseline	12.4 (8.03)	11.1 (6.38)	14.2 (9.20)	NA	NA
End of treatment	6.6 (4.33)	7.0 (6.98)	6.3 (5.12)	0.73 (−4.73 to 6.19)	1.53 (−3.55 to 6.60)
Follow-up	4.9 (3.60)	7.3 (8.82)	7.2 (6.72)	−1.74 (−6.55 to 3.07)	1.22 (−4.03 to 6.47)
ASI (0–64)					
Baseline	31.1 (9.92)	37.1 (9.56)	37.5 (12.91)	NA	NA
End of treatment	20.1 (10.29)	26.3 (10.56)	24.8 (13.95)	−1.25 (−11.50 to 9.00)	2.03 (−7.21 to 11.27)
Follow-up	19.6 (11.50)	20.8 (9.39)	20.8 (15.33)	3.30 (−7.75 to 14.34)	3.02 (−6.63 to 12.67)
Q-LES-Q-SF (14–70)					
Baseline	49.8 (6.20)	47.2 (8.88)	45.3 (11.63)	NA	NA
End of treatment	56.6 (3.20)	50.5 (9.32)	55.3 (7.69)	−1.28 (−6.93 to 4.37)	−6.19 (−11.59 to −0.79)
Follow-up	56.3 (5.17)	51.7 (8.76)	55.4 (7.94)	−2.14 (−6.81 to 2.52)	−5.23 (−10.65 to 0.18)

[a]Function score is the LS mean in the drug group minus LS mean in the placebo group, adjusted for drug group, visit, site, and drug group × visit, and baseline score. For all endpoints except Q-LES-Q-SF (by which increasing scores signify improvement), positive function scores imply greater numeric change in the placebo group than in the drug group.

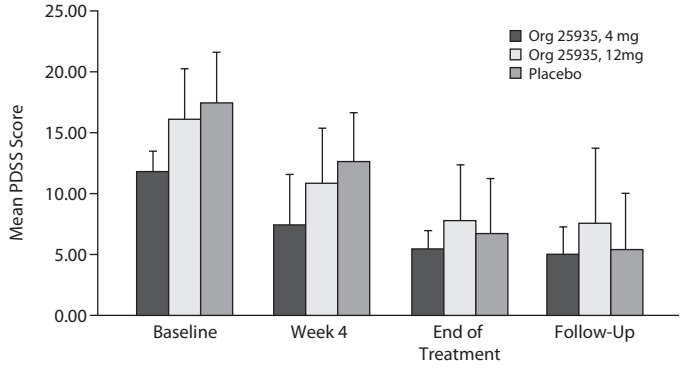
Abbreviations: ASI = Anxiety Sensitivity Index, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, NA = not applicable, PDSS = Panic Disorder Severity Scale, Q-LES-Q-SF = Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form, SIGH-A = Hamilton Anxiety Rating Scale-Structured Interview.

the single exception that Q-LES-Q-SF improvements were greater in the placebo group than in the 12-mg Org 25935 group at end of treatment (change from baseline 12-mg Org 25935: 3.7 ± 5.06, placebo: 10.8 ± 11.79; $P < .05$). This difference was also close to significant at follow-up ($P = .06$; see Table 2).

Safety and Tolerability

A single serious adverse event was reported for a patient who discontinued the trial and never received study medication. Five patients (3 in the 12-mg Org 25935 group and 1 each in the 4-mg and placebo groups) discontinued treatment due to adverse events. Org 25935 12-mg was associated

Figure 2. Mean PDSS Total Score at Each Visit



Abbreviation: PDSS = Panic Disorder Severity Scale.

Table 3. Adverse Events by Preferred Term, Total Incidence, and Incidence of Specific Events Occurring in ≥ 10% of Participants in Any Drug Group, All-Subjects-Treated Population

Adverse event, n (%)	Org 25935 4 mg (n = 11)	Org 25935 12 mg (n = 15)	Placebo (n = 14)
Any adverse event	8 (73)	12 (80)	5 (36)
Dizziness	2 (18)	7 (47)	0 (0)
Nausea	0 (0)	5 (33)	0 (0)
Headache	1 (9)	4 (27)	0 (0)
Visual impairment[a]	1 (9)	4 (27)	0 (0)
Vertigo	0 (0)	3 (20)	0 (0)
Vision blurred	0 (0)	2 (13)	1 (7)
Visual brightness	0 (0)	2 (13)	0 (0)
Derealization	0 (0)	2 (13)	0 (0)
Diarrhea	0 (0)	2 (13)	0 (0)
Rash	0 (0)	2 (13)	0 (0)
Fatigue	1 (9)	2 (13)	1 (7)

[a]Visual impairment investigator-reported terms: palinopsia, brief small brown spots in the periphery of the left visual field of both eyes, vision pulsating/abnormal vision, intermittently seeing spots, shaky vision, and improved visual acuity/abnormal vision.

with a greater incidence of adverse events than the other drug groups (Table 3); with nervous system events of dizziness and headache concluded to be dose-related. In addition, visual adverse events were reported much more frequently in the 12-mg Org 25935 group than in the 4-mg or placebo groups. Visual adverse events were generally brief in duration, all resolved without intervention, and no event was associated with objective ophthalmology findings. No clinically relevant, drug-related vital sign, electrocardiogram, or laboratory findings were noted.

DISCUSSION

To our knowledge, this is the first study to examine the effect of a glutamatergic compound other than DCS in a CBT augmentation paradigm. In the current trial, the glycine transporter inhibitor Org 25935 showed no benefit over placebo in augmenting CBT for panic disorder. No statistically significant differences were observed between Org 25935 (4 or 12 mg) and placebo on the PDSS or on any secondary efficacy measure, with the single exception that placebo was associated with greater improvements in quality of life (as measured by the Q-LES-Q-SF) than 12-mg Org 25935 at end of treatment. In addition, the 12-mg Org 25935 versus placebo comparisons for the PDSS and the Q-LES-Q-SF at follow-up were close to significant, in both cases favoring placebo. Overall, Org 25935 showed no safety issues at either dose but was much better tolerated at the 4-mg dose level than at the 12-mg dose level. These findings are in contrast to an earlier trial by Otto and colleagues[11] in which large effect sizes were observed favoring DCS over placebo and there were no reported drug-related adverse events.

Despite the fact that efficacy analyses for the current trial were underpowered due to the early termination of recruitment, we believe that our core study conclusions can be considered meaningful. The mean baseline and change from baseline PDSS scores for all patients combined are similar to that of the placebo group in the Otto et al study, suggesting that paradigm elements such as population and CBT effect were comparable. Importantly, although the endpoint PDSS scores in the placebo groups were similar between the 2 trials, the DCS-treated subjects in the Otto et al study had lower endpoint scores on average than did the Org 25935–treated subjects. This finding precludes the possibility that the results of the current trial can be explained by a CBT ceiling effect and further suggests that the integrity of the original treatment paradigm was preserved. Under the assumption of a 1.0 effect size, therefore, drug-placebo differences should have been visible even with this truncated sample size. In fact, treatment effects in many cases were in the unpredicted direction (ie, in favor of placebo) and therefore do not provide supportive evidence for the augmenting effects of Org 25935.

Other study limitations include group differences on most baseline efficacy assessments, which is the likely consequence of variability inherent to small samples. The placebo group clearly had more room for improvement than did the 4-mg Org 25935 group, particularly on the PDSS, and this could be reflected in the change from baseline score analysis. However, we note that 12-mg Org 25935 also did not outperform placebo, and here the baseline differences were far less profound.

Comment is warranted regarding the possibility that adverse events in the drug-treated groups may have impacted efficacy outcomes. The most frequent adverse events associated with Org 25935 in the current study (dizziness, nausea, and transient visual symptoms) are the very types of somatic symptoms that can lead to panic attacks in this population. It logically follows that any possible treatment benefit from drug augmentation may have been compromised by increased anxiety associated with drug-related adverse events.[43] However, we observed that, although such adverse events were reported much more frequently in the 12-mg group than in the 4-mg group, the numeric improvement on the PDSS was greater in the 12-mg group. Further, in exploratory post hoc analyses we found no difference in the magnitude of symptomatic improvement between completed study patients who had experienced these adverse events versus those who had not.

If we assume that the results of the current trial are true, we then must ask whether the negative finding implies a failure of the drug or the drug mechanism to influence extinction learning. Here, the answers are far less clear. Several glutamate compounds other than DCS have been shown to facilitate extinction learning in animal models, suggesting that fear extinction through alternate glutamate pathways is certainly possible.[44] Glycine uptake inhibition is associated with procognitive benefits in animal models of learning and memory.[26,27,29] However, until now it has not been tested in models specific to extinction learning, which has a unique and complex underlying neurobiological mechanism.[5] This target complexity is further extended by the rapidly growing body of work on interactions of receptor activity within the glutamate system. For example, recent work on glycine uptake inhibition raises new questions as to whether, in addition to its role in enhancing the NMDA response, it also plays a role in stimulation of inhibitory glycine receptors.[45–47] Also, the dose-response curve for the learning-enhancing effects of glutamate compounds, including DCS, is not clear, with some evidence that high doses of a partial agonist may impair learning.[48] Examining the data from the current trial in the context of this recent work, we must consider the finding that placebo showed a significant or close to significant benefit over Org 25935 on several endpoints and wonder whether Org 25935 may in fact be modulating the mechanism involved in CBT augmentation, but not in the hypothesized way. We propose that these findings add yet another question to the complex literature on NMDA activity in cognition and underscore the need for further research into glutamate modulation in human extinction learning.

Finally, we wish to address the finding that all groups showed significant symptomatic improvement regardless of the drug they received, and this improvement was maintained 1 month following the last CBT visit. This is not surprising, given the extensive body of literature supporting the efficacy of CBT for panic disorder, in which the mean effect size for treatments that involve cognitive restructuring plus interoceptive exposure (compared to alternative treatments or control conditions) is approximately 0.80.[1,49] Although the current trial lacks the interpretative benefit of a control psychotherapy condition, we expect that the improvements presented herein are not a simple reflection of nonspecific effects of treatment (ie, a placebo effect) but instead may attest to the efficacy of this brief 5-session intervention. This is supported by the fact that symptom severity levels at the end of treatment were similar in all 3 groups. That is, despite the notable group differences in baseline symptomatology and regardless of augmentation strategy, the CBT intervention resulted in comparable endpoint functioning. Other brief CBT interventions for panic disorder have also shown strong benefits.[50,51] The CBT treatment protocol utilized in the current trial is described elsewhere,[52] and research continues on brief intervention methods and other approaches that may render CBT more accessible to patients.

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Author contributions: Drs Nations, Smits, Tolin, Rothbaum, Hofmann, Lee, Schipper, Sjogren, Xue, Szegedi, Otto, and Ms Tart are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, interpretation of data. All authors drafted the manuscript and/or revised the manuscript for important intellectual content, and all authors provided final approval of the version to be published. These data have not been presented elsewhere.
Potential conflicts of interest: **Drs Nations, Schipper, Xue,** and **Szegedi** are employees of Merck & Co, Inc who may potentially own stock and/or hold stock options in the company. **Drs Sjogren** and **Lee** were employed by Merck at the time of this research. The affiliate institutions for **Drs Smits, Tolin, Rothbaum, Hofmann,** and **Otto** and **Ms Tart** received grant funding from Organon (now Merck & Co Inc.) for their work in this research. **Dr Rothbaum** is a part owner in Virtually Better, Inc. **Dr Otto** receives royalties from distribution of the Hamilton Anxiety Rating Scale-Structured Interview Version and has received speaker honoraria from the New England Educational Institute and the Connecticut Mental Health Association. **Dr Tolin** reports no additional financial or other relationship relevant to the subject of this article.
Funding/support: Organon (now Merck & Co, Inc) provided study drug (Org 25935) and financial support for the conduct of the study.
Acknowledgments: We would like to thank Yogesh Pande, MS (Merck Research Laboratories) for his expertise and contribution in statistical programming, and Kendra Sellers (Merck Research Laboratories) for her contribution in site management and monitoring. Mr Pande and Ms Sellers are employees of the corporate supporter.

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