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Abstract

Org 26576 acts by modulating ionotropic AMPA-type glutamate receptors to enhance glutamatergic neurotransmission. The aim of this Phase 1b study ($N=54$) was to explore safety, tolerability, pharmacokinetics, and pharmacodynamics of Org 26576 in depressed patients. Part I ($N=24$) evaluated the maximum tolerated dose (MTD) and optimal titration schedule in a multiple rising dose paradigm (range 100 mg BID to 600 mg BID); Part II ($N=30$) utilized a parallel groups design (100 mg BID, 400 mg BID, placebo) to examine all endpoints over a 28-day dosing period. Based on the number of moderate intensity adverse events reported at the 600 mg BID dose level, the MTD established in Part I was 450 mg BID. Symptomatic improvement as measured by the Montgomery-Asberg Depression Rating Scale was numerically greater in the Org 26576 groups than in the placebo group in both study parts. In Part II, the 400 mg BID dose was associated with improvements in executive functioning and speed of processing cognitive tests. Org 26576 was also associated with growth hormone increases and cortisol decreases at the end of treatment but did not influence prolactin or brain-derived neurotrophic factor. The quantitative electroencephalogram index Antidepressant Treatment Response at Week 1 was able to significantly predict symptomatic response at endpoint in the active treatment group, as was early improvement in social acuity. Overall, Org 26576 demonstrated good tolerability and pharmacokinetic properties in depressed patients, and pharmacodynamic endpoints suggested that it may show promise in future well-controlled, adequately powered proof of concept trials.

Keywords

Org 26576, AMPA receptor positive allosteric modulator, major depressive disorder, QEEG, emotional processing

Introduction

Despite the alarming prevalence (Wittchen et al., 2011) and increasing disability rates (Mathers and Loncar, 2006) among individuals with major depressive disorder (MDD), the landscape of available drug treatment options has remained relatively unchanged over the past 25 years. For the most part, current antidepressants enhance the function of noradrenergic and/or serotonergic neurotransmission in the brain. Up to 40% of patients who take these medications will fully remit from their depressive episode with short term treatment (Koscis, 2000; Rush et al., 2006), which in and of itself has major positive implications for public health. However, given the heterogeneity of the disease, the patients who do not respond adequately are subject to multiple new medication trials or augmentation strategies to address their symptoms (Practice Guideline, American Psychiatric Association, 2010) and a significant proportion of depressed patients are still considered chronic and treatment resistant (Crown et al., 2002). As a result, the field continues to pursue drugs of alternate mechanisms in order to address the growing need for more efficacious medications that also yield faster responses and better long-term maintenance. In addition, much of the research in recent years is

focused on uncovering biomarkers for therapeutic response in order to better predict which patients are most likely to respond to treatment (Bearden and Freimer, 2006).

A pharmacological target of increasing interest is glutamate, where multiple studies have demonstrated an association between

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dysregulation of the glutamatergic system and pathology of psychiatric diseases including mood disorders (Frye et al., 2006; Mitani et al., 2006; Hashimoto et al., 2007). AMPA receptor positive allosteric modulators, one of the three types of ionotropic glutamate receptors, are responsible for fast excitatory neurotransmission in the brain. Their activation has been reported to exert a variety of cellular effects including enhancing neurotrophic factor activity, particularly brain-derived neurotrophic factor (BDNF) (Lauterborn et al., 2000, 2003; Legutko et al., 2001), synaptic plasticity (Du et al., 2004), and neurogenesis (Bai et al., 2003). It has been suggested that modulation of these cellular activities may, in part, play a role in the mode of action for current antidepressant agents (Alt et al., 2006, O'Neil and Witkin, 2007). BDNF, in particular, is believed to play a critical role in mood disorders (Karege et al., 2002), and has been shown to increase in depressed patients after chronic treatment with some, but not all, monoaminergic antidepressants (Sen et al., 2008; Matriciano et al., 2009). Animal behavior models show that AMPA potentiators have rapid and subacute antidepressant effects (Li et al., 2001; Knapp et al., 2002). A fast growing body of work shows that NMDA antagonist ketamine has rapid, significant, and lasting effects on depression symptoms (Berman et al., 2000, Zarate et al., 2006) and, importantly, subsequent animal work suggests that ketamine's action may be mediated in part by enhanced AMPA activation (Maeng et al., 2008). In humans, similar AMPA modulating compounds have resulted in mixed outcomes for acute schizophrenia (Noorbala et al., 1999; Marenco et al., 2002), cognitive deficits in schizophrenia (Goff et al., 2001, 2008), and attention-deficit/hyperactivity disorder (Adler et al., 2012), though there are no published reports of AMPA modulators in MDD.

Org 26576 (chemical name: [9aS]-8,9,9a, 10-tetrahydro-5H, 7Hpyrido [3,2-f] pyrrolo[2,1-c] [1,4]oxazepin-5-one) belongs to a novel class of compounds referred to as AMPA-PAMs (alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid receptor positive allosteric modulators), which act by modulating ionotropic AMPA-type glutamate receptors to enhance glutamatergic neurotransmission (Lynch 2006; Arai and Kessler, 2007). In vitro, Org 26576 potentiates AMPA receptor mediated activity in rat neuronal preparations (Erdemli et al., 2007). The compound has no direct agonist activity and its effects are only seen in the presence of the agonist glutamate. In vivo, acute administration of Org 26576 enhances AMPA-mediated hippocampal neuronal activity in rats (Bursi et al., 2011) and chronic administration has been shown to facilitate hippocampal neuronal proliferation and survival (Su et al., 2009) which in some animal models mediates the behavioral effects of antidepressant medications (Warner-Schmidt and Duman, 2007). In rats, Org 26576 is active in depression and cognitive impairment models: it significantly increases reinforcements earned in the DRL-72 (differential reinforcement of low rate) paradigm (data on file at Merck), reverses phencyclidine (PCP)-induced deficits in novel object recognition (data on file at Merck), and improves spatial reference learning and retrieval in the Morris water maze task (Hamlyn et al., 2009).

In a Phase 1 trial evaluating Org 26576 in healthy volunteers ($N=36$), Org 26576 was tolerated at doses up to 225 mg BID; the most frequent adverse events were nausea, dizziness, somnolence, feeling drunk and postural dizziness (Nations et al., 2012). Org 26576 was rapidly absorbed and disposed with a terminal half-life not longer than 3 hours. Peak concentrations as well as time to peak concentrations increased sub-proportionally and underwent

a time delay, suggesting a dose-dependent partially saturated absorption process. No regimen effects were observed, though a food effect on maximum concentration was noted. Analysis of neuroendocrine variables showed that mean levels of cortisol, prolactin and growth hormone appeared to be higher than placebo (most evident at 1 hour post-dose) upon multiple dosing of 100–400 mg Org 26576 (data on file at Merck).

The current study was designed as a Phase 1b trial and was undertaken with the primary goal of informing Phase 2 dose selection by determining the maximum tolerated dose, general safety and tolerability, and pharmacokinetic properties (PK) of Org 26576 in patients diagnosed with major depressive disorder. An overview of the tolerability and PK evaluations is presented here, with additional details provided elsewhere (Nations et al., 2012). The focus of the current report will be on secondary pharmacodynamic endpoints which were included in this Phase 1b trial to explore the effect of Org 26576 on depressive symptomatology, cognition, BDNF and endocrine responses.

In addition, this trial sought to examine the ability of several promising biomarkers to predict clinical response to Org 26576. Frontal cordance in the theta frequency band is an index derived from quantitative electroencephalogram (QEEG) and is thought to reflect higher perfusion in the anterior cingulate cortex, a structure linked to the pathophysiology of depression (Asada et al., 1999; Leuchter et al., 1999; Pizzagalli et al., 2003; Pizzagalli, 2010). In several studies, early reductions in frontal cordance at Week 1 or 2 were able to predict response to various monoaminergic antidepressant treatments but not to placebo at treatment endpoint (Cook and Leuchter, 2001; Cook et al., 2002; Leuchter et al., 2002; Bares et al., 2008, 2010). Another emerging marker is Antidepressant Treatment Response (ATR; Aspect Medical Systems, now Covidien, Mansfield, Massachusetts, USA) which incorporates several different frontal measurements utilizing metrics derived from theta and alpha bands to yield an index that successfully predicted drug response in the Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression study (BRITE-MD; Leuchter et al., 2009a, 2009b). Interestingly, preliminary data also suggests that QEEG may be helpful in identifying brain changes that are associated with non-specific treatment response (i.e. placebo response), and that these indexes are distinct from those that identify probable medication responders (Leuchter et al., 2002).

We further examined emotional processing as an early predictive marker for symptomatic change. The collective research in this field suggests that change in emotional processing, specifically reductions in negative biases and increases in positive biases, may be a new mechanism for studying the potential efficacy of antidepressant treatments (see Pringle et al., 2011 for a review). With few exceptions, these studies have shown that the accuracy of facial emotion recognition (i.e. social acuity) decreases for negative faces and increases for positive faces both acutely and with chronic dosing with antidepressant medications. Further, recent data suggests that emotional processing changes early in treatment can significantly predict eventual clinical response in depressed patients (Tranter et al., 2009). As with QEEG, most of the emotional processing work published to date has been conducted using monoaminergic compounds. It is largely unknown how novel compounds might influence facial emotion recognition. Given the small study sample and preliminary nature of these evaluations, all pharmacodynamic measures and biomarkers were examined in an exploratory fashion, i.e. no a priori hypotheses were established.

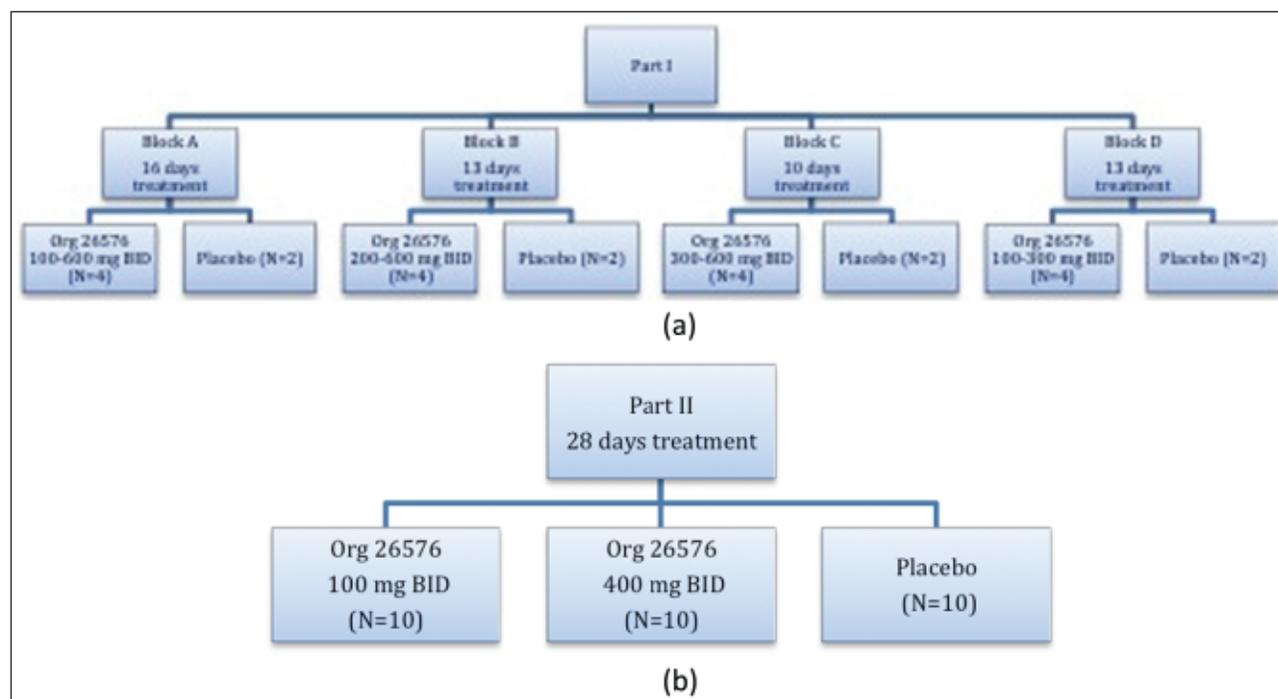


Figure 1. Trial design.

Methods

Design

This study was conducted in two successive parts (Figure 1(a) and (b)). Part I was a double-blind, randomized, placebo controlled multiple rising dose evaluation in 24 patients. Four sequential cohorts of six patients each were evaluated in the dosing range of 100–600 mg BID with titration steps every three days, for a total exposure duration of 10–16 days depending on titration schedule. Cohorts A, B, and C started at progressively higher doses, all rising to 600 mg BID; cohort D evaluated cerebrospinal fluid (CSF) pharmacokinetics at the lower end of the dosing range in order to determine the extent to which Org 26576 is able to cross the human blood brain barrier. Starting doses were selected based on the findings of a previous study in healthy volunteers (Nations et al., 2012), and objectives were to determine the maximum tolerated dose, optimal titration schedule, safety and tolerability, pharmacokinetics and pharmacodynamics of Org 26576.

Part II utilized a 30-patient double-blind, randomized, placebo-controlled, parallel group design which evaluated two dose levels of Org 26576 for 28 days (10 subjects assigned to 100 mg BID, 10 subjects assigned to 400 mg BID, and 10 subjects assigned to placebo), with objectives to evaluate tolerability, plasma pharmacokinetics, and pharmacodynamics over an extended 28-day treatment period. The doses in Part II were selected based on tolerability results from Part I.

Participants

Patients were recruited by PAREXEL's Early Phase Unit in Glendale, California, USA in conjunction with the California

Clinical Trials Medical Group between September 2007 and December 2008. This trial was conducted in accordance with the principles of Good Clinical Practice and was approved by the center's institutional review board prior to the commencement of study activities. Patients were recruited primarily through advertisements and referrals, and all were compensated for participation. All study participants signed an informed consent form before any screening evaluations were performed.

As this was principally an early safety and PK trial, entry criteria were focused on the inclusion of very healthy but at least mildly depressed individuals. Selected patients were male or female, ages 18–65 years, and diagnosed according to DSM-IV-TR with MDD. Current depressive episodes were mild to severe without psychotic features, no more than two years in duration, with a total score of at least 9 but not more than 20 on the Quick Inventory for Depression Symptomatology – Clinician Rated (QIDS-C). Patients who had received antidepressant treatment at adequate dose and duration in the current episode were excluded. Eligible patients were otherwise healthy and medically stable; were taking no concurrent psychotropic medications; and had no history of bipolar disorder, psychosis, post traumatic stress disorder, obsessive compulsive disorder, or eating disorder. Patients with a 6-month history of substance dependence (not including nicotine), current substance abuse, or a positive screening or admission urine drug/alcohol test were excluded.

Procedures

Screening procedures included psychiatric interview by a licensed psychiatrist or psychologist, and confirmation of primary and comorbid diagnoses using the Mini International Neuropsychiatric Interview (MINI; version 5.0.0, 2006; Sheehan et al., 1998).

Patients were assessed for symptom severity with the Quick Inventory of Depression Symptomatology – Clinician Rated (QIDS-C; Rush et al., 2003). Screening safety assessments included medical history, physical exam, electrocardiogram (ECG), electroencephalogram (EEG), vital signs, and clinical laboratory testing.

Eligible patients were randomized to receive Org 26576 or placebo via a centrally-generated randomization list. Org 26576 and placebo were prepared as indistinguishable capsules containing placebo, 50 or 100 mg Org 26576 for oral administration. An unblinded on-site pharmacist was responsible for preparing study medication according to the randomization list and for dispensing blinded medication to clinical staff for patient administration. In Part I, the randomization ratio was 2:1, Org 26576 to placebo, with dose ranging from 100–600 mg BID, depending on starting dose and titration schedule. Patients in Part II were randomized to receive Org 26576 100 mg BID, Org 26576 400 mg BID, or placebo in a 1:1:1 ratio. All patients were treated in an inpatient setting, with confinement beginning two days before the first dose and ending the day after the final dose. Diet, smoking, and physical activity were controlled; concomitant medication use was significantly restricted; alcohol and recreational drugs were prohibited. Doses were taken after a meal at approximately 8 am and 8 pm.

Assessments

Safety and tolerability. Tolerability was evaluated via daily adverse event assessment. Safety was assessed by measuring vital signs, ECG, and the Beck Scale for Suicidal Ideation (BSS; Beck et al., 1988) on a regular basis. In addition, enhanced EEG and laboratory assessments were conducted to closely monitor human safety of Org 26576 in areas of concern. Given the purported potential for neurotoxicity associated with glutamatergic compounds (e.g. Swann et al., 1993), safety EEGs were conducted every 3–7 days in order to screen for human pro-convulsive effects associated with Org 26576. Safety EEG data were collected in a resting state with eyes open and closed, with photic stimulation, and with 3 minutes hyperventilation. Further, based on previous toxicology work with Org 26576 showing liver toxicity in dogs (but not rodents; data on file at Merck), liver enzymes were thoroughly monitored daily during study Part I and, after no liver concerns were identified in Part I, twice weekly thereafter.

Pharmacokinetics. Plasma samples were collected pre-dose and at eleven time points through 12 hours post-dose (but before the pm dose) every three days in Part I. Eight samples were collected in the same time frame at Days 1, 4, and 28 in Part II. In Block D of Part I, continuous CSF was collected in fractions of 30 minutes each starting at 2 hours prior to through 12 hours following the morning dose on Day 1 and Day 10.

Psychiatric symptomatology. Severity of depression was measured using the Montgomery-Asberg Depression Rating Scale (MADRS; Montgomery and Asberg, 1979), a 10-item clinician-rated measure of depression with a total score ranging from 0–60, and the single-item Clinical Global Impression of Severity (CGI-S) and Improvement (CGI-I) scales (Guy, 1976). The MADRS was administered at baseline followed by every 2–3 days in Part I and was administered at baseline, Day 2, Day 4, and weekly thereafter in Part II. The CGI was administered weekly in both study

parts. Treatment response was defined as $\geq 50\%$ change in MADRS from baseline to week 4, and remission was defined as MADRS ≤ 10 at week 4 (Zimmerman et al., 2004).

Cognitive functioning and social acuity. Computerized cognitive testing was administered in Part II only using a CNS-Vital Signs battery (CNSVS; Chapel Hill, North Carolina, USA; Gualtieri and Johnson, 2006) which included tests of verbal memory (word list recall), visual memory (symbol recall), processing speed (symbol digit coding), attention and executive function (shifting attention task), verbal reasoning (e.g. ‘a is to b, and x is to _’), and working memory (4-part N-back continuous performance test). The battery also included a social acuity component called the Perception of Emotions Test (POET). In this test, 48 faces are presented randomly covering a range of positive and negative emotions (sad, angry, calm, and happy), and subjects are tasked with selecting the accurate emotion word that represents the face presented as quickly as possible. The full 30-minute cognitive testing battery was administered at Day 1 prior to first dose, and at Days 7, 14, and 28. All subjects completed two testing sessions prior to baseline in order to stabilize practice effects.

Neuroendocrine parameters and BDNF. Serum neuroendocrine levels (cortisol, prolactin, and human growth hormone (hGH)) were measured in both study parts in order to explore the effects of Org 26576 on markers that may be indicative of action on glutamate receptors (Gonzales et al., 1999a, 1999b, Hergovich et al., 2001; Aguilar et al., 2005). BDNF was measured in both serum and, for a single Part I cohort, CSF. Blood samples were collected pre-dose and at multiple time points post-dose every three days in Part I and at Day 1, Day 4, and Day 27 in Part II. After collection, samples were kept at ambient temperature for 30 minutes to allow coagulation, at which point they were centrifuged for 15 minutes at approximately 2000 g. CSF samples were collected on Day 1 and Day 10 only, and after collection were centrifuged for the period necessary to spin down any existing blood cells. Plasma and CSF samples were stored at -80°C until the end of each study block, when they were shipped on dry ice to the bioanalysis laboratory.

QEEG. Quantitative EEG was evaluated in Part II only at Baseline and Week 1. Nineteen-channel digital EEGs were recorded using the Neuroscan Scan Monitor (Compumedics Ltd) with a sampling rate of 250 Hz per channel. Scan 4.3 software allowed for recording and review of EEG with user selectable viewing montages. QEEG was collected under resting conditions with eyes closed. A subset of EEG channels (four channel EEG recordings) were collected using the Aspect Medical NS-5000 system with a sampling rate of 128 Hz per channel. The full head EEGs were used to calculate cordance, an EEG metric that relates absolute and relative power measures. The Cordance technology was developed at UCLA (University of California, Los Angeles, CA, USA) and licensed by Aspect Medical Systems, Inc. (see Cook et al., 2002 for details). In addition, 4-channel EEGs were separately collected from the subjects using Aspect’s NS-5000 System. Baseline and Week 1 EEGs were used to calculate Aspect’s ATR index, an EEG metric derived from the pair of frontotemporal EEGs (At1-Fpz, At2-Fpz; see Leuchter et al., 2009a for details).

Bioanalysis. Org 26576 and its internal standard were isolated from ethylene diamine tetra-acetic acid (EDTA) plasma by solid

phase extraction. Liquid chromatography-mass spectrometry (LC-MS) using turbo electrospray ionization in multi reaction monitoring mode was performed in order to quantify the concentration of Org 26576. The assay has been validated in the range of 0.2–200 ng/mL. Analysis of Org 26576 in CSF was undertaken exploratively with a non-validated LC-MS method. Serum samples for hormone analyses were analyzed using a validated fluoroimmunoassay. CSF and serum samples for BDNF were analyzed using a validated immunoassay (ELISA). Laboratory assessments were conducted in full compliance with Good Laboratory Practice.

Analytic plan

Safety, tolerability, and pharmacokinetic endpoints. Safety endpoints were evaluated using summary and descriptive statistics for the all-subjects-treated population (AST: all patients who received at least one dose of study medication). The MTD, determined based on Part I data, was defined a priori as the dose one step below the minimum intolerated dose (MID), where MID was the dose at which $\geq 50\%$ of subjects experienced multiple moderate adverse events or a single severe adverse event, or the dose at which a serious adverse event occurred in one or more subjects.

Pharmacokinetic parameters were evaluated using summary and descriptive statistics for the all-subjects-pharmacokinetically-evaluable (ASPE) group, which included those subjects for whom at least one PK parameter could be calculated, and who did not have any protocol violations interfering with PK.

Pharmacodynamic endpoints. All pharmacodynamic outcome evaluations (efficacy, cognition including social acuity, neuroendocrine variables and BDNF), were undertaken using summary and descriptive statistics for the AST population. Median concentrations were plotted using time concentration curves for Part II endocrine and BDNF values. Given the fact that this was principally a safety trial, which was not powered to detect significant treatment group differences on pharmacodynamic endpoints, no statistical testing was performed.

Predictors of symptomatic change. Nineteen-channel digital EEGs were sent to UCLA's Laboratory of Brain, Behavior and Pharmacology to be inspected by EEG technicians blinded to the analysis. Here, periods of artifact-free, drowsy-free EEG were

identified and then used by Aspect for cordance analysis. The week 1 QEEG predictors of medication response evaluated were: (1) change from baseline in prefrontal theta cordance and (2) Aspect's ATR index. These were evaluated first in the active treatment dose group (both dose groups combined) then in each individual dose group. The baseline QEEG predictor of placebo response was based on a logistic model called Baseline Placebo Predictor (BPR), which included frontocentral theta cordance, the QIDS component of Late Insomnia, and the accuracy on the Symbol Digit Coding Task from the CNSVS battery. SPSS (rev 12.0, SPSS, Inc.) was used to analyze the dataset, $p < 0.05$ considered statistically significant. P -values were not controlled for multiple comparisons.

The relationship between early improvements in speed or accuracy on the POET test and endpoint symptomatic response as measured by the MADRS was evaluated following the example of Tranter and colleagues (2009). Pearson's product moment correlation coefficients were calculated and tested for (1) change from baseline to Day 7 and 14 on facial recognition accuracy (positive, negative, and all emotions combined), and (2) change from baseline to endpoint on MADRS total score. The same analyses were repeated using reaction times instead of accuracy.

Results

Patient characteristics

A total of 130 patients provided informed consent and were screened for the study. Of these, 76 were screen failures, the majority of whom, due to stringent entry criteria, were excluded based on abnormal laboratory tests. In Part I, 24 patients were randomized, 22 (92%) of whom completed treatment. In Part II, 30 patients were randomized and 28 (93%) patients completed. All 54 patients received at least one dose of study medication, qualifying them for the AST population.

Baseline patient characteristics are presented in Table 1. During Part I, most patients randomized were male (75%) due to an early exclusion of females of childbearing potential until animal reprotoxicity studies could be completed. The gender distribution in Part II was more balanced (57% male, 43% female). Patients were primarily white (61%), on average relatively young (age mean 35.4 ± 11.3 years), moderately depressed (QIDS-C mean 15.2 ± 2.4), and were most often diagnosed with

Table 1. Participant and illness characteristics at screening, all-subjects-treated population.

	Part I		Part II		
	Org 26576 (<i>n</i> =16)	Placebo (<i>n</i> =8)	Org 26576 100 mg BID (<i>n</i> =10)	Org 26576 400 mg BID (<i>n</i> =10)	Placebo (<i>n</i> =10)
Age, mean (SD)	36.7 (10.3)	34.1 (12.7)	38.3 (14.4)	35.6 (12.8)	31.1 (6.5)
Male, <i>n</i> (%)	11 (68.8)	7 (87.5)	6 (60)	6 (60)	5 (50)
White, <i>n</i> (%)	9 (56.3)	6 (75.0)	6 (60)	8 (80)	4 (40)
QIDS-C score, mean (SD)	14.0 (2.8)	15.8 (2.0)	15.0 (2.5)	15.3 (1.1)	17.0 (1.9)
Duration of present episode <1 year, <i>n</i> (%)	16 (100)	6 (75)	6 (60)	7 (70)	7 (70)
Duration of present episode 1–2 years, <i>n</i> (%)	0 (0)	2 (25)	4 (40)	3 (30)	3 (30)
First episode MDD, <i>n</i> (%)	2 (12.5)	3 (37.5)	2 (20)	3 (30)	3 (30)
Recurrent MDD, <i>n</i> (%)	14 (87.5)	5 (62.5)	8 (80)	7 (70)	7 (70)

MDD: major depressive disorder; QIDS-C: Quick Inventory of Depression Symptomatology – Clinician Rated; SD: standard deviation.

Table 2. Adverse events by preferred term, total incidence and incidence of specific events occurring in $\geq 20\%$ of participants in any treatment group, all-subjects-treated population.

	Part I		Part II		
	Org 26576 ^a (n=16)	Placebo (n=8)	Org 26576 100 mg BID (n=10)	Org 26576 400 mg BID (n=10)	Placebo (n=10)
	n (%)	n (%)	n (%)	n (%)	n (%)
Any adverse event	16 (100)	7 (87.5)	10 (100)	9 (90.0)	9 (90.0)
Abnormal dreams	0	2 (25.0)	1 (10.0)	2 (20.0)	1 (10.0)
Back pain	1 (6.3)	2 (25.0)	1 (10.0)	1 (10.0)	0
Disturbance in attention	1 (6.3)	2 (25.0)	0	0	0
Dizziness	7 (43.8)	2 (25.0)	5 (50.0)	2 (20.0)	2 (20.0)
Fatigue	0	0	1 (10.0)	3 (30.0)	0
Feeling drunk	1 (6.3)	0	2 (20.0)	4 (40.0)	0
Headache	11 (68.8)	4 (50.0)	5 (50.0)	4 (40.0)	5 (50.0)
Insomnia	5 (31.3)	2 (25.0)	1 (10.0)	1 (10.0)	3 (30.0)
Irritability	0	0	0	2 (20.0)	0
Muscle twitching	4 (25.0)	0	0	1 (10.0)	0
Nasal congestion	0	2 (25.0)	0	0	0
Nausea	10 (62.5)	2 (25.0)	3 (30.0)	3 (30.0)	1 (10.0)
Palpitations	3 (18.8)	1 (12.5)	0	0	2 (20.0)
Post lumbar puncture syndrome ^b	3 (18.8)	2 (25.0)	0	0	0
Rash	0	0	2 (20.0)	0	0
Sedation	2 (12.5)	0	2 (20.0)	1 (10.0)	2 (20.0)
Sensory disturbance	2 (12.5)	1 (12.5)	0	2 (20.0)	0
Somnolence	7 (43.8)	4 (50.0)	4 (40.0)	5 (50.0)	5 (50.0)

^aDose variable depending on treatment day and study block. Range was 100–600 mg BID.

^bPost lumbar puncture syndrome reported as spinal headache; reported in block D only (five of six total patients) where cerebrospinal fluid (CSF) was sampled.

recurrent depression (76%) currently experiencing an acute episode of less than one year duration (78%). Two subjects in Part I and no subjects in Part II were diagnosed with a comorbid Axis I disorder.

Safety, tolerability, and pharmacokinetics

Safety and tolerability. No treated patients experienced a serious or severe adverse event. Two subjects discontinued the trial due to adverse events: one subject taking Org 26576 in Part I discontinued due to akathisia at the highest dose (600 mg BID), and one subject taking placebo in Part II discontinued due to tension headache. Based on Part I data, the MTD was considered to be 450 mg BID with an optimal starting dose of 200 mg BID. Treatment-emergent adverse events reported most frequently in the active treatment group ($\geq 25\%$ of subjects in either study part and at least 2x greater incidence than in the placebo group) were insomnia, dizziness, nausea, muscle twitching, fatigue, and feeling drunk (Table 2). There were no clinically significant drug-related laboratory (including liver enzymes), vital sign, ECG, or EEG findings in the study (see also Nations et al., 2012).

Pharmacokinetics. Plasma PK evaluation showed that for the different titration schemes in Part I, similar exposure values were found for the highest Org 26576 dose (600 mg). In Part II, for the

100 mg BID treatment group, the mean dn-C_{max} and dn-area under the curve (AUC) values for Days 4 and 27 were approximately 30% higher than for Day 1. For the 400 mg BID treatment group, similar mean dn-C_{max} and dn-AUC values were found for all days (including Day 1 with a single dose of 200 mg). The mean dose-normalized exposure values for the 400 mg BID group tended to be somewhat higher than those for the 100 mg BID group. Time to maximum concentration was the same at Day 4 regardless of dose (1.75 hours), but was slightly longer at Day 27 in the 400 mg BID group (2.0 hours) than in the 100 mg group (1.5 hours). Mean half-life ranged from 2.1–2.5 hours in both dose groups. No major deviations from dose proportionality and time independence of kinetics of Org 26576 were observed in this study in the titration schemes and dose range tested (see also Nations et al., 2012). The mean Org 26576 exposure and concentration values in plasma and CSF were similar, both on Day 1 (100 mg single dose) and on Day 10 (300 mg steady state). CSF T_{max} followed plasma T_{max} by approximately 15 minutes with single doses and by approximately 1.5 hours with multiple doses (see also Bursi et al., 2011).

Pharmacodynamics

Psychiatric symptomatology. Average MADRS scores in the current trial decreased from baseline regardless of treatment

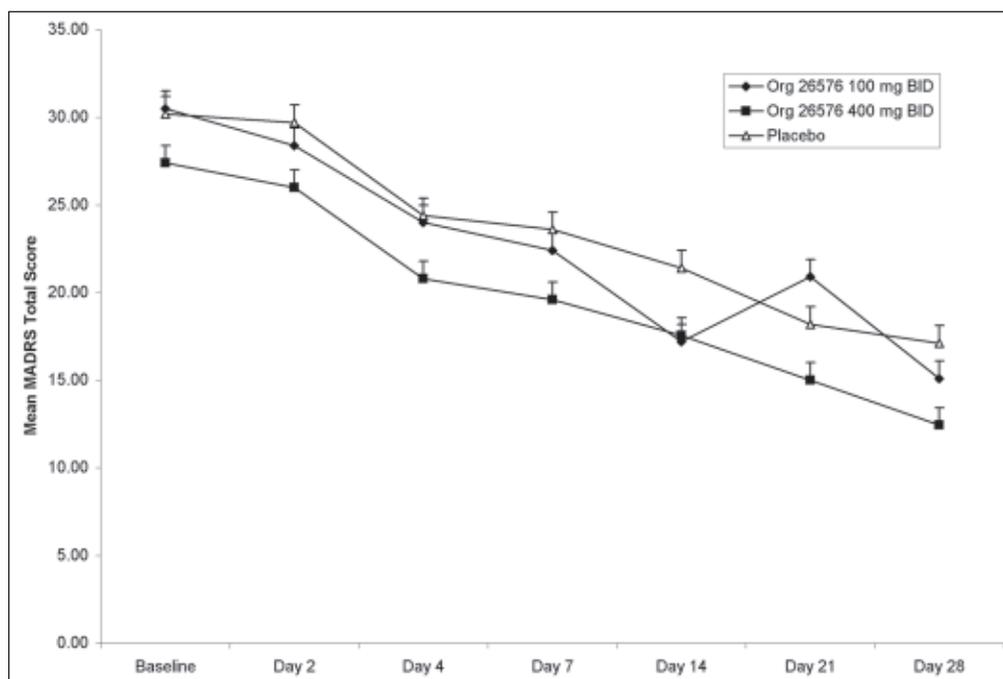


Figure 2. Mean Montgomery-Asberg Depression Rating Scale (MADRS) score at every visit by treatment group (Part II).

group, dose, or titration schedule. Across all blocks combined in Part I, Org 26576 was associated with numerically greater change from baseline to endpoint MADRS scores than placebo (Org 26576 -13.19 ± 10.18 ; placebo -10.75 ± 9.88); however, results were highly variable depending on study block and no consistent drug vs placebo patterns were evident. In Part II, both Org 26576 dose groups showed a numerically greater change from baseline than placebo at every time point with the exception of Day 21 (Figure 2). There were no clear or consistent differences between drug and placebo in MADRS response or remission rates, change from baseline on CGI severity scores, or in CGI improvement rates. All efficacy data are presented in Table 3.

Cognitive functioning and social acuity. The neurocognitive index (NCI), a standardized overall measure of cognitive functioning, showed very modest treatment group differences. Calculation of individual cognitive domain scores (raw scores incorporating specific test endpoints) showed no drug/placebo differences on domain score change from baseline to Day 28 for most parameters, with a few notable exceptions. While executive functioning changed minimally from baseline to Day 28 in the placebo group (1.8 ± 10.05 points), it was much improved at Day 28 in the 100 mg BID group (23.8 ± 26.14) and in the 400 mg BID group (14.2 points ± 23.65), which reflects effect sizes (ES) relative to placebo (Cohen's *d*) of 1.01 and 0.77 for the 100 mg BID and 400 mg BID groups, respectively. To examine the contribution of baseline differences to treatment effects in this domain, we excluded (post hoc) five subjects (three subjects in the 100 mg BID Org 26576 group and two subjects in the 400 mg BID Org 26576 group) who, while performing adequately on other measures, performed extremely poorly on this test at baseline. Exclusion of these five subjects minimized baseline group

differences in executive functioning but did not fully eliminate the treatment effect (Org 26576 100 mg BID vs placebo: ES=0.72; Org 26576 400 mg BID vs placebo: ES 0.17). For the domains of processing speed, sustained attention, and working memory, change from baseline average scores were numerically greater in the 400 mg BID group than in the 100 mg BID or placebo groups. In particular, the difference between the 400 mg BID group and the placebo group on processing speed yielded an ES of 0.88. There were no consistent findings in any domain that suggested Org 26576 was associated with deterioration in cognitive functioning. Cognitive testing data are presented in Table 4.

Overall, there were no clear drug/placebo or dose-related patterns in the change from baseline social acuity domain score (Table 4). Furthermore, Org 26576 did not change accuracy or reaction times in a dose-related fashion for positive, negative, or all emotional faces combined. However, one trend emerged consistently at every time point: the average reaction time for all emotional faces combined decreased from baseline in the 400 mg BID group but not the 100 mg BID or placebo groups. This was also true for negative faces at every time point and positive faces at Day 7. Social acuity data are presented in Table 5.

Neuroendocrine parameters and BDNF. Median hGH concentrations, observed within the time interval ranging from 1 hour to 2 hours after dosing in Blocks A through D of Part I, were highly variable. In Block A, they were below 0.5 mIU/L. In the remaining blocks, they ranged between 0.2 mIU/L and 23 mIU/L. For the placebo subjects they were below lower limit of quantification (LLOQ) (0.1 mIU/L). Visual inspection of the Part II time concentration curves shows that median hGH concentration was clearly higher for the Org 26576

Table 3. Efficacy scale results, baseline and change from baseline, all subjects treated population.

Part I	Part II		Part II			
	Org 26576 ^a (n=16)	Placebo (n=8)	Org 26576 100 mg BID (n=10)	Org 26576 400 mg BID (n=10)	Placebo (n=10)	
MADRS, mean (SD)			MADRS, mean (SD)			
Baseline	31.06 (5.67)	29.63 (4.72)	Baseline	30.50 (4.06)	27.40 (4.84)	30.20 (3.71)
Day 2, CFB	-5.25 (7.74)	-6.38 (7.63)	Day 2, CFB	-2.10 (4.15)	-1.40 (7.28)	-0.50 (4.48)
Day 4, CFB	-9.69 (7.12)	-8.50 (7.91)	Day 4, CFB	-6.44 (5.53)	-6.60 (6.19)	-5.80 (6.36)
Day 7, CFB	-10.63 (7.60)	-9.00 (8.76)	Day 7, CFB	-8.10 (5.97)	-7.80 (9.17)	-6.60 (5.21)
Day 10, CFB	-13.08 (12.25)	-10.33 (9.83)	Day 14, CFB	-13.30 (4.27)	-9.67 (9.91)	-8.80 (7.35)
Endpoint, CFB ^b	-13.19 (10.18)	-10.75 (9.88)	Day 21, CFB	-9.60 (5.44)	-12.22 (9.65)	-12.00 (5.68)
			Day 28, CFB	-15.40 (6.40)	-14.78 (11.72)	-12.67 (9.35)
			Endpoint, CFB ^b	-15.40 (6.40)	-13.70 (11.57)	-13.30 (9.04)
MADRS response at end-point, N (%) ^{b,c}	7 (43.8)	2 (25.0)	MADRS response at end-point, N (%) ^{b,c}	5 (50.0)	4 (40.0)	5 (50)
MADRS remission at end-point, N (%) ^{b,c}	4 (25.0)	1 (12.5)	MADRS remission at end-point, N (%) ^{b,c}	3 (30.0)	3 (30.0)	4 (40)
CGI - Severity, mean (SD)			CGI - Severity, mean (SD)			
Baseline	4.63 (0.89)	4.50 (0.76)	Baseline	4.10 (0.32)	3.90 (0.32)	4.10 (0.32)
Day 7, CFB	-0.75 (1.18)	-0.75 (0.89)	Day 7, CFB	-0.30 (0.48)	-0.80 (1.14)	-0.30 (0.48)
Endpoint, CFB ^b	-1.19 (1.42)	-0.75 (1.04)	Day 14, CFB	-0.80 (0.63)	-0.89 (1.36)	-0.60 (0.70)
			Day 21, CFB	-0.40 (0.52)	-1.11 (1.27)	-1.00 (0.94)
			Day 28, CFB	-1.30 (0.67)	-1.44 (1.13)	-1.33 (1.41)
			Endpoint, CFB ^b	-1.30 (0.67)	-1.30 (1.16)	-1.40 (1.35)
CGI-Improvement at end-point, N (%) ^{b,d}	6 (37.5)	2 (25.0)	CGI-Improvement, N (%) ^{b,d}	8 (80.0)	6 (60.0)	6 (60)

CFB: change from baseline; CGI: clinical global impression; MADRS: Montgomery-Asberg Depression Rating Scale; SD: standard deviation.

^aPart I dose variable depending on treatment day and study block. Range was 100 mg BID to 600 mg BID. Time points relevant to all Part I study blocks are presented.

^bObserved case data are presented for all visits except Endpoint, where last observation carried forward is presented.

^cResponse defined as $\geq 50\%$ decrease from baseline to endpoint on MADRS total score. Remission defined as ≤ 10 at endpoint on MADRS total score.

^dCGI Improvement defined as a score of 1 (very much improved) or 2 (much improved).

groups than for the placebo group within the time interval of 1 hour to 4 hours post-dosing (Figure 3). Median serum cortisol concentrations in Part I, observed at around 2 hours post-dose were approximately 80% higher in the Org 26576 group than in the placebo group. In Part II, for both Org 26576 groups, the median cortisol serum concentrations at around 2 hours post-dose were approximately 20% higher on Day 1 and approximately 40% lower on Day 27 than for the placebo group (Figure 4). No effect of Org 26576 on serum prolactin was observed, nor was there an effect on BDNF levels in serum (Figures 5 and 6) or CSF.

Predictors of symptomatic change

QEEG. All available, artifact-free data for patients who completed the trial were used for analysis of each metric at each time point. Therefore the number of subjects available for analysis of Week 1 prediction using change in prefrontal cordance or ATR and baseline prediction using frontocentral cordance were 23, 25, and 26 respectively. There was little change in cordance in either response or non-response groups for medication treatment. However, ATR was significantly higher in responders compared with non-responders in the pooled

medication group (60.3 ± 12.1 vs 49.3 ± 2.2 , $p=0.036$). Although ATR was also higher in responders than in non-responders in each dose group (100 mg BID: 55.1 ± 7.8 vs 48.1 ± 5.5 , $p=0.16$ and 400 mg BID: 67.1 ± 15.0 vs 50.8 ± 8.3 , $p=0.12$), this difference did not achieve statistical significance (Figure 7). ATR was not significantly different between responders and non-responders in the placebo group (41.1 ± 11.1 vs 50.3 ± 18.5 , $p=0.413$). The accuracy of ATR to predict response was similar in both the 100 mg BID (78%) and 400 mg BID (71%) groups. Post hoc graphical inspection revealed no relationship between ATR and Org 26576 Cmax or AUC values. None of the predefined variables at baseline (frontocentral theta cordance, QIDS-C late insomnia scores, Symbol Digit Coding scores or the combination algorithm BPR) significantly predicted placebo response at endpoint.

Social acuity. For the 400 mg BID group only, there was a statistically significant positive relationship between change from baseline to Day 14 on positive faces items correct and change from baseline to endpoint MADRS scores ($r=0.66$, $p=0.037$), and for change from baseline to Day 14 on all faces combined and change from baseline to endpoint MADRS scores ($r=0.77$, $p=0.009$).

Table 4. Cognitive test battery results at baseline and change from baseline in Part II, all-subjects-treated population.

Domain	Change from baseline											
	Baseline score			Day 7			Day 14			Day 28		
	100 mg BID Org 26576 (n=10)	400 mg BID Org 26576 (n=10)	Placebo (n=10)	100 mg BID Org 26576 (n=10)	400 mg BID Org 26576 (n=10)	Placebo (n=10)	100 mg BID Org 26576 (n=10)	400 mg BID Org 26576 (n=10)	Placebo (n=10)	100 mg BID Org 26576 (n=10)	400 mg BID Org 26576 (n=10)	Placebo (n=10)
Composite memory	89.7 (7.07)	92.1 (9.15)	93.2 (10.50)	-3.8 (15.24)	-3.5 (10.80)	-1.9 (10.19)	-5.3 (8.63)	-1.4 (6.55)	-5.9 (10.47) ^a	-4.6 (10.20)	-8.3 (14.23) ^a	-8.2 (12.12) ^a
Executive function	29.0 (29.78)	36.4 (22.17)	50.9 (9.09)	17.0 (25.13)	13.1 (16.24)	9.9 (9.11)	19.5 (19.96)	15.0 (21.12)	10.9 (9.21) ^a	23.8 (26.14)	14.2 (23.65) ^a	1.8 (10.02) ^a
Processing speed	47.4 (8.06)	47.5 (13.89)	59.6 (12.29)	6.6 (8.19)	8.2 (4.92)	7.3 (6.48)	3.9 (10.33)	8.5 (10.72)	6.3 (8.69) ^a	-1.6 (19.36)	8.8 (6.02) ^a	1.8 (10.05) ^a
Reasoning	3.5 (6.98)	5.2 (6.83)	4.0 (5.91)	0.8 (2.66)	0.5 (4.95)	0.3 (6.33)	0.9 (4.70)	0.7 (5.76)	1.8 (3.56) ^a	-0.3 (4.32)	2.1 (5.51) ^a	3.4 (4.80) ^a
Social acuity	7.2 (4.21)	8.2 (2.57)	7.9 (4.12)	-0.8 (5.33)	-0.8 (2.78)	-1.1 (5.17)	2.6 (3.27)	0.3 (2.79)	-0.4 (2.92) ^a	0.8 (4.13)	-0.9 (2.37) ^a	-1.8 (2.39) ^a
Sustained attention	19.1 (10.35)	24.4 (7.46)	28.7 (7.01)	0.3 (20.12)	2.6 (7.62)	-1.7 (5.54)	-4.3 (18.50)	0.4 (7.07)	0.9 (2.20) ^a	-6.7 (21.38)	1.6 (10.96) ^a	-5.4 (8.20) ^a
Verbal memory	48.2 (4.61)	46.7 (6.67)	49.3 (5.44)	-0.6 (11.09)	-1.9 (7.55)	-1.5 (8.15)	-2.0 (5.33)	-0.5 (3.31)	-5.2 (7.05) ^a	-1.6 (5.99)	-1.9 (7.62) ^a	-5.7 (6.86) ^a
Visual memory	41.5 (4.67)	45.4 (5.52)	43.9 (6.23)	-3.2 (5.53)	-1.6 (5.32)	-0.4 (3.84)	-3.3 (6.57)	-0.9 (4.89)	-0.7 (4.33) ^a	-3.0 (5.48)	-6.4 (8.59) ^a	-2.6 (6.82) ^a
Working memory	6.1 (4.89)	7.4 (4.22)	9.6 (4.35)	-1.3 (7.96)	2.5 (6.02)	-1.4 (3.84)	0.0 (5.50)	1.8 (4.76)	0.4 (3.24) ^a	-2.0 (6.60)	1.3 (5.70) ^a	-2.4 (4.03) ^a
Neuro-cognitive Index	88.3 (11.26)	92.1 (13.10)	96.1 (10.95)	1.7 (16.79)	3.0 (9.12)	0.2 (5.33)	2.6 (9.36)	4.4 (6.26)	1.1 (7.57) ^a	-0.3 (13.52)	1.7 (11.32) ^a	-4.7 (8.38) ^a

SD: standard deviation. ^an=9; observed case data. Data are presented as mean (SD).

Table 5. Perception of emotions test results at baseline and change from baseline in Part II, all-subjects-treated population.

Test name	Change from baseline											
	Baseline score ^a			Day 7			Day 14			Day 28		
	100 mg BID Org 26576 (n=10)	400 mg BID Org 26576 (n=10)	Placebo (n=10)	100 mg BID Org 26576 (n=10)	400 mg BID Org 26576 (n=10)	Placebo (n=10)	100 mg BID Org 26576 (n=10)	400 mg BID Org 26576(n=10)	Placebo (n=10)	100 mg BID Org 26576 (n=10)	400 mg BID Org 26576 (n=10)	Placebo (n=10)
Average reaction time for correct on negative emotions (ms)	1015.5 (395.19)	1337.8 (433.69)	984.1 (395.71)	137.4 (447.03)	-94.7 (279.49)	44.6 (548.11)	240.5 (583.12)	-102.1 (439.33)	5.4 (236.27) ^a	293.4 (521.66)	-161.2 (272.20) ^a	95.6 (338.61) ^a
Average reaction time for correct on positive emotions (ms)	1008.0 (204.29)	1175.9 (214.04)	929.4 (340.60)	15.1 (237.90)	-50.6 (196.76)	-7.4 (454.78)	120.2 (301.29)	14.1 (224.65)	31.4 (231.14) ^a	86.4 (221.02)	20.1 (195.31) ^a	26.0 (281.09) ^a
Average reaction time for correct on perception of emotions task (ms)	1036.6 (223.01)	1235.3 (257.00)	953.0 (354.62)	46.2 (221.25)	-41.8 (114.07)	20.9 (491.52)	146.2 (335.86)	-7.0 (161.55)	25.9 (153.21) ^a	157.6 (260.15)	-48.6 (109.94) ^a	53.7 (232.28) ^a
Number correct on negative emotions	4.3 (2.00)	5.1 (1.29)	4.6 (1.90)	0.9 (1.97)	-0.3 (0.95)	0.0 (2.79)	1.0 (1.49)	-0.3 (0.67)	-0.1 (0.93) ^a	0.9 (1.85)	0.1 (1.17) ^a	-0.3 (0.87) ^a
Number correct on positive emotions	4.6 (1.78)	5.3 (0.82)	5.3 (1.89)	0.2 (2.53)	-0.1 (1.52)	-0.7 (2.83)	1.4 (1.78)	0.0 (0.67)	-0.4 (1.13) ^a	0.7 (2.11)	-0.1 (0.78) ^a	-0.7 (1.73) ^a

SD: standard deviation. Data are presented as mean (SD).
^an=9; observed case data.

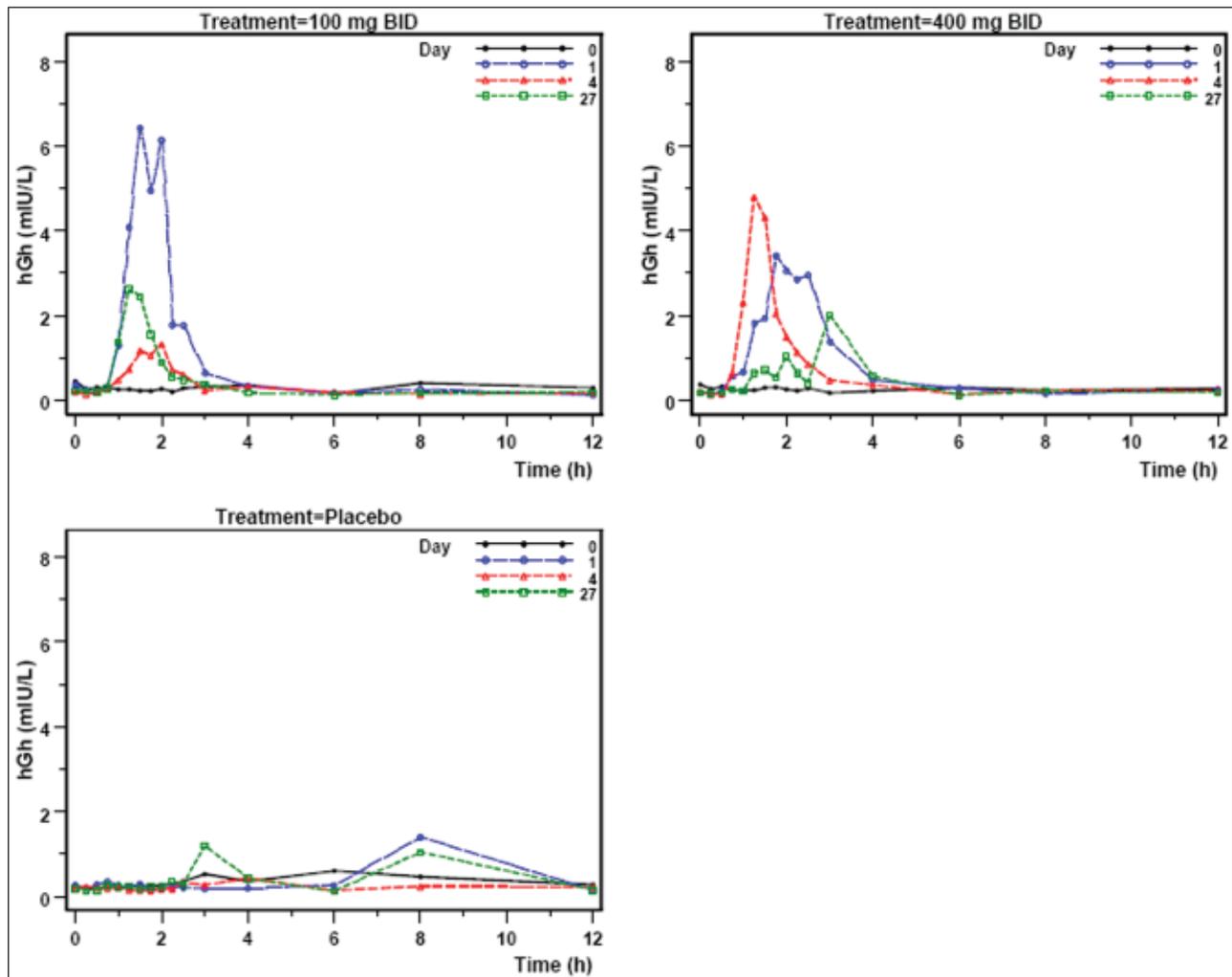


Figure 3. Median serum human growth hormone (hGh) concentration by day and treatment group (Part II).

Discussion

The current trial was undertaken in advance of Phase 2 efficacy trials with the primary objectives to determine the maximum tolerated dose, optimal titration schedule, and overall safety of Org 26576 in patients diagnosed with major depression. From the Part I multiple rising dose paradigm, it was concluded that Org 26576 was well tolerated up to 450 mg BID with a starting dose of 200 mg BID. No clinically relevant safety issues were observed at any dose in either study part up to the full 28 days of treatment. Org 26576 plasma and CSF pharmacokinetics were also characterized, showing that titration scheme does not significantly change overall exposure at the terminal dose, that plasma and CSF exposure is comparable, and that the kinetics of Org 26576 are generally dose proportional and time independent in the dose range tested.

All patients in the current trial were treated as inpatients for the full duration of the study so that safety and tolerability could be closely monitored. This design provided a unique opportunity to explore a number of relevant pharmacodynamic endpoints, not as a basis for development decisions but in order to build preliminary confidence in the compound's ability to

modulate its target. We therefore explored not only symptomatic change, but we also evaluated the effect of Org 26576 on endpoints thought to be associated with glutamate modulation or AMPA activity (e.g. cognition, BDNF, and neuroendocrine variables) and we evaluated whether early changes in QEEG and social acuity were predictive of a later clinical response to treatment.

All treatment groups, including placebo, showed a mean improvement in depressive symptomatology as measured by the MADRS. Changes from baseline scores were numerically greater in the Org 26576 groups than in the placebo group; however, a clear dose effect on efficacy was not apparent. Approximately half of the participants were classified as drug responders at the endpoint in Part II regardless of treatment group assignment and we expect that the non-specific effects of treatment, such as a structured inpatient setting and significant clinician-patient interaction time, likely contributed to the high response rates in all groups. It should also be noted that selected subjects were on average healthier and less severely depressed than might be expected for a trial in which efficacy signal detection is the primary objective. For these reasons, and as is true for all other pharmacodynamic

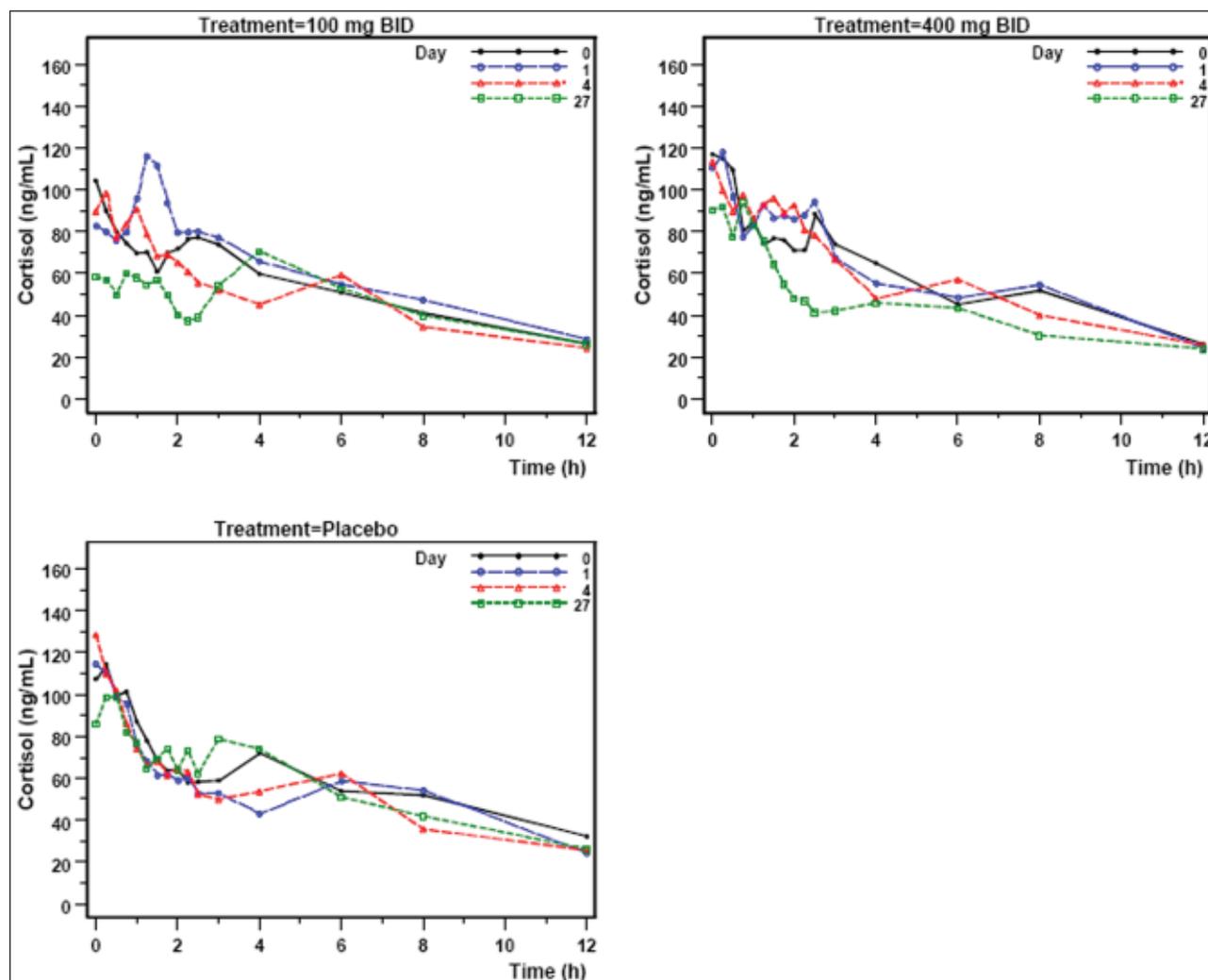


Figure 4. Median serum cortisol concentration by day and treatment group (Part II).

endpoints, these results must be interpreted with extreme caution given the exploratory nature of this small trial.

Org 26576 was associated with what could be considered clinically relevant cognitive improvement in the domains of executive functioning (both 100 and 400 mg BID groups) and speed of processing (400 mg BID), where ES ranged from 0.77–1.01 (Cohen, 1988). Despite the fact that the Org 26576 groups were clearly showing more baseline cognitive difficulties on average than the placebo group in several domains, post hoc examination of the data suggests that neither baseline differences nor a ceiling effect in the placebo group can fully account for the greater improvement in the drug group. The cognitive effects in the current study appear to exceed those reported for stabilized schizophrenic patients (Goff et al., 2001, 2008) and we cautiously propose that they lend early confidence that AMPA modulation in general, and Org 26576 specifically, may improve cognitive functioning in those domains most relevant to depression (see Austin et al., 2001). Although the accuracy of facial emotion recognition did not improve with treatment in any group, reaction time did improve in the 400 mg BID group without a corresponding

decrease in accuracy. Whether this reflects general improvement in social acuity similar to that which has been observed in dedicated emotional processing trials (Pringle et al., 2011), or instead is the simple result of a speed of processing improvements in the 400 mg BID group, is not entirely clear. Importantly, despite relatively high rates of insomnia and fatigue associated with Org 26576 in this trial, drug-related deterioration in cognitive functioning was not observed.

In the current trial, Org 26576, but not placebo, raised average growth hormone levels within the time interval of 1–4 hours after dosing. This is consistent with previous animal work showing that ionotropic glutamate receptor activation results in a stimulation of growth hormone release in both young and adult animals (see Aguilar et al., 2005 for a review). Further, consistent with the effects of Org 26576 on serum cortisol in healthy volunteers (data on file at Merck), dosing with Org 26576 resulted in higher cortisol levels than in the placebo group on Day 1. However, cortisol levels were lower on Day 27 in the Org 26576 group than in the placebo group. The reason for the acute to chronic dosing effects on cortisol are not entirely clear. Previous

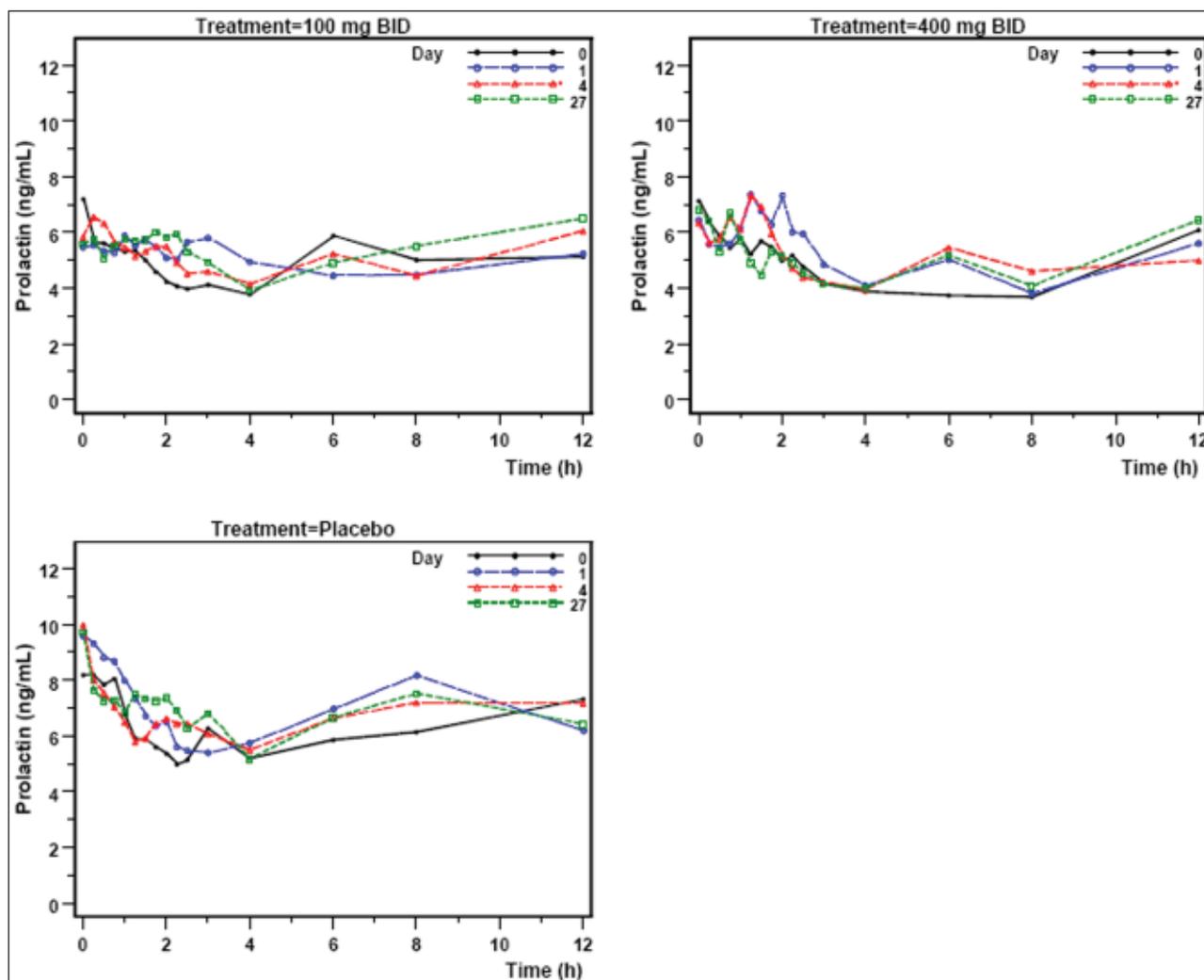


Figure 5. Median serum prolactin concentration by day and treatment group (Part II).

trials have shown antidepressant effects on lowering cortisol, though results are variable depending on specific drug and duration of dosing (see Ahmed et al., 2011). In contrast with previous work, both prolactin and BDNF levels were unchanged by Org 26576. The lack of Org 26576 effect on prolactin, a sensitive marker for D2 and dopamine (Ben-Jonathan and Hnasko, 2001), suggests that there is minimal to no downstream regulation of this neurotransmitter system. The absence of observable increases in BDNF in the current trial is not entirely surprising in the light of more recent findings of Matriciano and colleagues (2009), who examined three effective monoaminergic compounds and measured serum BDNF levels at baseline and after five weeks and six months of treatment. Sertraline was associated with increased BDNF levels after five weeks; venlafaxine after six months, and escitalopram not at all. It is possible, therefore, that 28 days of treatment was insufficient to show measurable effects on BDNF in depressed patients.

Finally, and perhaps among the most interesting of the findings in the current trial, QEEG analysis confirmed that Week 1 ATR, but not the change in prefrontal theta cordance, was able to

significantly predict clinical response after four weeks of Org 26576 treatment. The ATR finding is consistent with previous work using monoaminergic compounds (Leuchter et al., 2009a, 2009b) and provides further evidence that ATR may be an early marker for clinical response, assuming that future studies demonstrate the anti-depressant efficacy of Org 26576. In addition, we found that early social acuity improvements significantly predicted clinical response at endpoint in the Org 26576 400 mg BID group. Clearly these preliminary findings should not be over-interpreted; however, we feel it worth noting that the marker was significant for two different endpoints (positive faces and all faces combined) and was relatively robust even in the context of treatment with a novel compound and employing a much simpler test paradigm than has been used in previous dedicated work (see Tranter et al., 2009; Pringle et al., 2011). At minimum, these findings lend additional support to the idea that social acuity changes may ultimately offer practitioners a window into clinical response not typically detectable so early in treatment.

Despite the exploratory nature of the current trial as well as the inherent limitations to interpretability associated with small

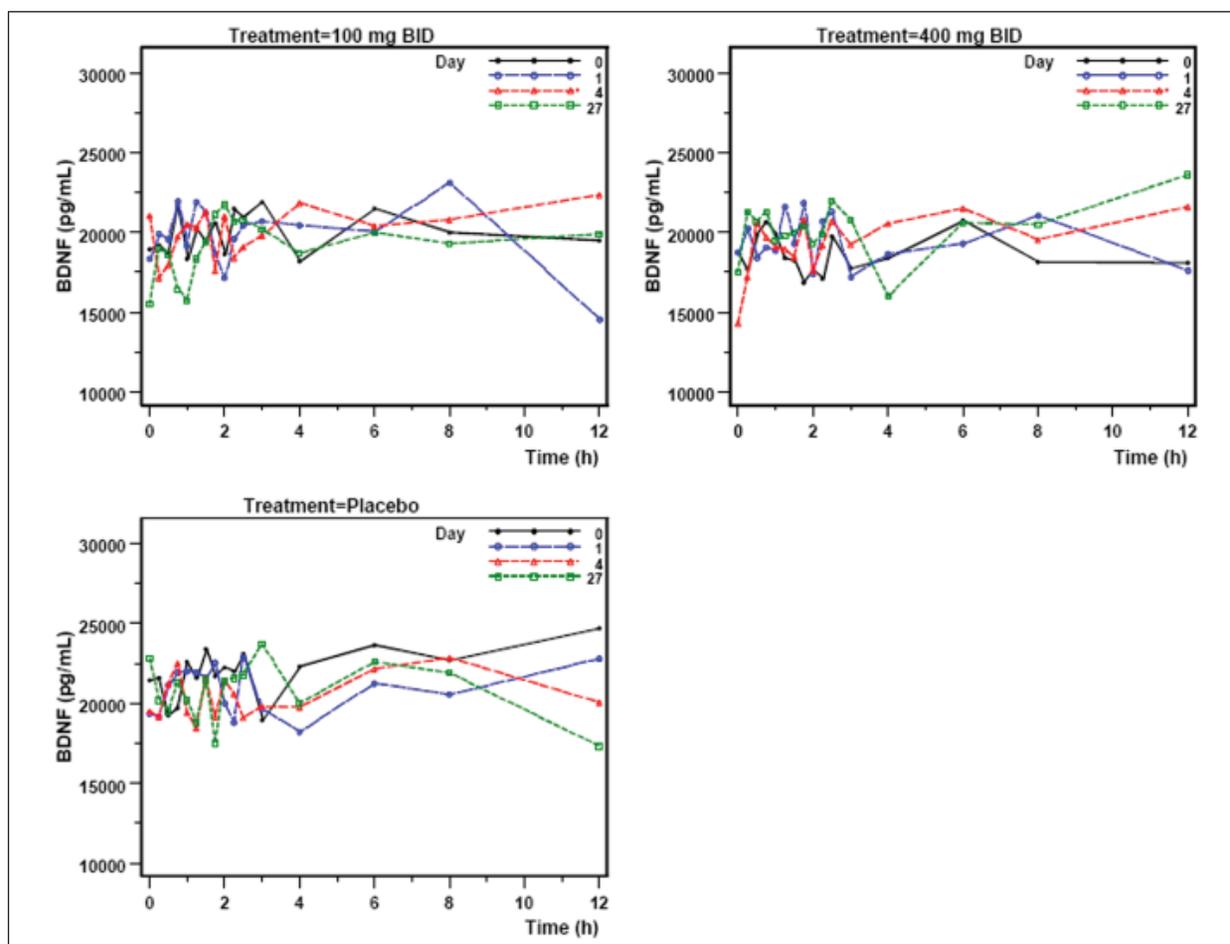


Figure 6. Median serum brain-derived neurotrophic factor (BDNF) concentration by day and treatment group (Part II).

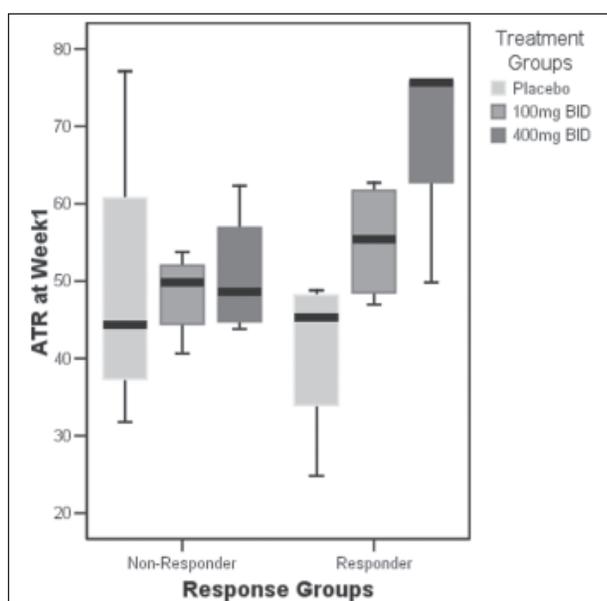


Figure 7. QEEG Antidepressant Treatment Response (ATR) in treatment responders vs non-responders by treatment group (Part II). Note: the box and whisker format shows the lower and upper quartiles and the median (the box) within the full range of the distribution of data points (bars).

samples, we believe that the following conclusions were firmly established: Org 26576 is well tolerated in the target patient population, it crosses the human blood brain barrier and leads to cerebral activation, and it shows at least some endocrine activity that is consistent with glutamate modulation. Albeit far less conclusive, the effects of Org 26576 on depressive symptomatology and cognition are encouraging for future Phase 2 research, where proof of concept can be evaluated in an appropriately powered outpatient efficacy trial that includes patients that are more representative of the depressed population at large. Finally, the current trial provides additional evidence in favor of two specific early markers of treatment response, and supports our optimism that the field will continue to develop not just better treatments but also better ways to guide our treatments in the interest of reducing the debilitating effects of depression on individuals' and public health.

Trial registration: clinicaltrials.gov Identifier NCT00610649.

Conflict of interest

Drs. Nations, Lee, and Mr. Pande, were employed by Merck Sharp & Dohme Corp. (Whitehouse Station, NJ, USA) at the time of this research. Drs. Bursi, Schipper, and Ruigt were employed by Merck Sharp & Dohme Oss BV (Oss, the Netherlands) at the time of this research. Dr. Dogterom is a current employee of Merck Sharp & Dohme Oss BV (Oss, the

Netherlands). The employers of Drs. Ereshefsky and Gertsik (California Clinical Trials Medical Group, Inc.), Dr. Greenwald and Mr. Zrakat (Covidien, formerly Aspect Medical Systems, Inc.) and Dr. Johnstone (Q-Metrx) were paid by Organon (now Merck) for their work on this trial.

Funding

Organon (now Merck) provided the study drug (Org 26576) and financial support for the conduct of the study.

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