Randomized, Double-Blind, Placebo-Controlled Trial of the $mGlu_{2/3}$ Negative Allosteric Modulator Decoglurant in Partially Refractory Major Depressive Disorder

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ABSTRACT

Objective: To assess putative antidepressant and procognitive effects of decoglurant, a selective metabotropic glutamate receptor type 2/3 ($mGlu_{2/3}$) negative allosteric modulator, as adjunctive treatment to selective serotonin reuptake inhibitors and/or serotonin-norepinephrine reuptake inhibitors (SSRIs/SNRIs) in patients with partially refractory major depressive disorder (MDD), diagnosed using *DSM-IV-TR* criteria.

Methods: This randomized, placebo-controlled, double-blind, multicenter phase 2 trial consisted of 4 weeks' screening, 6 weeks' treatment, and 8 weeks' follow-up between September 2011 and June 2014. Individuals with Montgomery-Åsberg Depression Rating Scale (MADRS) score ≥ 25 and Clinical Global Impressions–Severity of Illness scale score ≥ 4, despite up to 2 adequate trials of an SSRI/SNRI and compliance confirmed by positive SSRI/SNRI blood levels, were randomized to decoglurant 5 mg (n = 101), 15 mg (n = 102), or 30 mg (n = 55) daily or placebo (n = 99) as adjunct to ongoing treatment with 1 SSRI/SNRI. An adaptive design was used with an interim analysis after 30 patients in each group had received 6 weeks' treatment. The primary outcome variable was change in MADRS total score from baseline to end of treatment. Primary assessments were performed by fully blinded centralized raters.

Results: Of 357 participants, 310 completed 6 weeks' treatment. At 6 weeks, no significant differences between any active treatment arm and placebo in reducing MADRS total score or response or remission rates were observed. Decoglurant exerted no significant effects on Cambridge Neuropsychological Test Automated Battery cognitive accuracy and cognitive speed composite scores or on secondary measures of mood and functioning. A relatively high placebo response was observed, which may have constrained the ability to detect treatment effects. No deaths occurred; few patients reported serious adverse events.

Conclusions: Decoglurant was well tolerated overall but did not exert any antidepressant or procognitive effects.

Trial Registration: ClinicalTrials.gov identifier: NCT01457677

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Major depressive disorder (MDD) exerts a significant personal, economic, and societal burden.[1–3] Pharmacologic intervention currently involves treatment with monoamine reuptake inhibitors (eg, selective serotonin reuptake inhibitors [SSRIs], serotonin-norepinephrine reuptake inhibitors [SNRIs]), and atypical antipsychotics, in conjunction with psychotherapy. However, a substantial proportion of patients do not respond to first- or second-line treatment.[4]

The clinical presentation of MDD includes impairments in cognitive functions, which, contrary to previous beliefs, represent a key feature of MDD that is largely independent of the severity of classical depressive symptoms.[5–8] Most available antidepressants—with the possible exception of vortioxetine[9]—have not been shown to improve cognitive deficits beyond those accounted for by depressive symptoms. Novel antidepressants that also effectively ameliorate cognitive deficits associated with MDD are needed.

While classic antidepressants mediate their effect primarily through monoamines, growing evidence supports the treatment of MDD through modulation of dysregulated glutamate neurotransmission.[10–13] Of specific interest, as therapeutic targets in MDD, are the metabotropic glutamate receptor type 2 ($mGlu_2$) receptors—presynaptic auto-inhibitory receptors that are highly expressed in the PFC, hippocampus, amygdala, and nucleus accumbens—with preclinical research suggesting that $mGlu_2$ antagonists have antidepressant and procognitive effects.[10,14–17] Indeed, a highly selective $mGlu_{2/3}$ antagonist (RO4432717) that was used as a tool compound reversed $mGlu_{2/3}$ agonist induced cognitive deficits and improved long-term memory in preclinical assays.[5] Another selective, potent non-competitive $mGlu_{2/3}$ negative allosteric modulator, decoglurant (RG1578),[18] was found to reduce the anhedonia index in a chronic mild stress model in rats and to rescue scopolamine-induced deficits in executive function and attention in non-human primates (D.U., unpublished data, 2015). We therefore hypothesized that in individuals

Clinical Points

- Many patients with major depressive disorder (MDD) do not respond to first- or second-line therapies, and current treatments do not improve the associated cognitive deficits.
- In patients with partially treatment-resistant MDD, the metabotropic glutamate receptor type 2/3 ($mGlu_{2/3}$) antagonist decoglurant was well tolerated but did not have an antidepressant or procognitive effects in combination with selective serotonin reuptake inhibitors or serotonin-norepinephrine reuptake inhibitors.

diagnosed with MDD, decoglurant may restore normal glutamate transmission, thus reducing depressive and cognitive symptoms.

In initial safety studies in healthy volunteers, decoglurant had a good safety and tolerability profile (EudraCT trial no. 2009–011624-62). A potential procognitive effect was also supported by its reversal of scopolamine-induced cognitive deficits in healthy volunteers (EudraCT trial no. 2009–014678-17).

The primary objective of the current trial was to assess putative antidepressant and procognitive effects of decoglurant versus placebo as adjunctive treatment to SSRI/SNRI therapy in individuals with MDD and inadequate response to antidepressant treatment. The aim was to focus on patients considered to have an optimum chance of responding to a novel adjunctive treatment option, specifically those with relatively recent–onset disease failing no more than 2 previous treatments.

METHODS

Trial Design and Patients

This randomized, placebo-controlled, double-blind, phase 2 trial consisted of a 4-week screening period, 6-week treatment period, and 8-week follow-up period (ClinicalTrials.gov identifier: NCT01457677). It was conducted between September 2011 and June 2014 at 72 sites in Canada, Austria, Germany, Russia, Ukraine, Slovakia, South Africa, and the United States following Guidelines for Good Clinical Practice.[19] The protocol was approved by the health authorities of each country and ethics committees of each site. All participants gave written informed consent.

Patients with a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*), diagnosis of MDD without psychotic features, who continued to have depressive symptoms despite 1 or 2 adequate trials with an SSRI or SNRI at doses equal to or greater than the accepted dose according to the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire,[20] were eligible. The index depressive episode had to have started within 1 year of screening, and treatment dose and duration were verified from the treating physician and/or pharmacy records. Other key inclusion criteria were scores of ≥ 25 on the Montgomery-Åsberg Depression Rating Scale (MADRS)[21] and ≥ 4 on the Clinical Global Impressions–Severity of Illness scale (CGI-S),[22] as assessed by fully blinded centralized raters. Compliance with current SSRI/SNRI treatment was assessed with blood tests; if levels of the respective antidepressant were undetectable, patients were not enrolled. Only 1 SSRI/SNRI was continued during the trial. Medications used to treat stable medical conditions other than depression were allowed, providing doses were stable (see Supplementary Table 1 for full inclusion and exclusion criteria).

Randomization

After screening, participants were randomized into 4 groups: decoglurant at a once-daily dose of 5 mg, 15 mg, or 30 mg or placebo, all in addition to existing permitted medications (see Supplementary Table 2 for details on the administration of study medication).

Randomization codes generated by the sponsor were administered by an interactive voice or web-based response system. Randomization was stratified by cognitive impairment, sex, and geographic region. Cognitive impairment was initially defined as a score of 1 standard deviation below the normative mean of the mean combined score of the attentional (Rapid Visual Processing [RVP]), memory (Paired Associates Learning [PAL]), and executive (Stockings of Cambridge [SOC]) tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB).[23] After recruitment of 79 participants, the threshold was lowered to 0.5 SD below the normative mean as too few patients met the original criterion. Before this change, 13 patients were categorized as "not cognitively impaired"; subsequently, they would have been categorized as "cognitively impaired."

Endpoints

The primary efficacy endpoint was the MADRS total score, assessed by centralized, fully blinded raters using the MADRS-SIGMA revision.[24]

Secondary mood and functioning endpoints included the CGI-S and CGI-Improvement scale (CGI-I)[22] and participant-rated measures comprising the Inventory of Depressive Symptomatology–Self-Report 30-item version ($IDS\text{-}SR_{30}$),[25] Cognitive and Physical Functioning Questionnaire (CPFQ),[26] Sheehan Disability Scale (SDS),[27] Quality of Life Enjoyment and Satisfaction Questionnaire–Short Form (Q-LES-Q-SF),[28] and Patient-Rated Global Improvement (PGI), adapted from the clinician-rated CGI-S.[22]

Cognitive impairment was assessed with the CANTAB cognitive test battery,[23] which included Motor Screening (MOT); RVP; Delayed Matched to Sample (DMS); Emotional Recognition Task (ERT); PAL; SOC at screening, or One-Touch Stockings of Cambridge (OTS, at baseline and day 42); and Attention Shifting Test (AST). A factor analysis—using 2 key parameters for each test of the CANTAB battery (excluding the ERT)—of the data obtained at baseline in the current study, and a simultaneously conducted study of basimglurant in treatment-refractory MDD,[13] demonstrated two key factors: one loading on accuracy measures of all

tests and one loading on measures of reaction time across all tests (see Supplementary Table 3 for exploratory factor analysis). Thus, an a priori decision was made before study completion to use calculated cognitive accuracy and speed composite scores as the primary cognitive outcome variables (see Supplementary Table 4 for details of the tasks tested for CANTAB).

Safety data were collected through clinical and neurologic examinations; recording of adverse events (AEs); clinician-administered rating scales (Columbia–Suicide Severity Rating Scale,[29] Extrapyramidal Symptom Rating Scale–Abbreviated,[30] and Young Mania Rating Scale [item 1 when indicated to follow up on AEs only][31]), and measurement of vital signs, electrocardiograms, and laboratory parameters.

Assessments

Centralized raters assessed illness severity at screening using the MADRS, and they administered the MADRS and CGI-S at baseline and at all visits during treatment and follow-up periods via telephone in the patient's native language. Site raters (a local trial-site physician, nurse, clinical psychologist, or social worker with certified psychiatric practice and ≥ 2 years' experience administering standardized rating scales in MDD) also administered the MADRS and CGI-S at baseline and week 6 and the CGI-I at week 6 (see Supplementary Figure 1 for details of the trial design).

At screening, assessments included the centrally administered MADRS and CGI-S, the patient-rated IDS-SR_{30}, and the CANTAB battery. Primary and secondary outcome assessments were conducted at baseline, weekly during the 6-week treatment period, and at weeks 8, 10, and 14 during the follow-up period (Supplementary Figure 1). The CANTAB battery was administered at screening, baseline, and week 6. A limited CANTAB battery including only the MOT, RVP, and PAL was administered at day 7.

Statistical Analysis

The primary efficacy variable—change in MADRS total score from baseline to end of treatment—was analyzed using a mixed-effects model for repeated measures (MMRM) that included independent variables of the fixed effects of treatment, stratification variables, geographical region, assessment weeks relative to the first dose of study medication (ie, time), and treatment-by-time interaction, along with the continuous effect of baseline MADRS total score. An unstructured variance-covariance matrix was applied to model the within-patient errors. A treatment-by-time interaction contrast was used to estimate the difference between each decoglurant dose and placebo in mean change from baseline to week 6 of treatment. Response was defined as ≥ 50% improvement from baseline in MADRS total score and remission as MADRS total score ≤ 10. The primary analysis was conducted for the per-protocol (PP) population (ie, all randomized patients with valid baseline and 6-week MADRS total scores [centralized rating] who were not excluded because of protocol violation criteria) with no imputation for missing values. The 95% confidence intervals (CIs) of treatment difference and nominal *P* value (no adjustment for multiple comparisons) are reported for each dose of decoglurant. As a sensitivity analysis, the primary efficacy variable was also analyzed using the intention-to-treat (ITT) population (all patients randomly assigned to treatment) via MMRM or last observation carried forward imputation. A "MADRS interest-activity" score[32] was calculated by summing the scores of the Concentration Difficulties, Lassitude, and Inability to Feel items.

Analyses of variance and covariance were used to investigate the effect of decoglurant on the secondary efficacy endpoints using the PP and ITT populations. Subgroup analyses based on categorical variables were performed on selected secondary efficacy endpoints. Ordered categorical data were analyzed using the Wilcoxon signed rank test and binary data using the Fisher exact test.

To minimize exposure to potentially ineffective treatment, and associated side effects, a prespecified Bayesian interim futility analysis was conducted after 30 participants in each treatment arm had completed 6 weeks' treatment. It was decided before the start of the study to stop 1 dose arm if the probability of reaching an effect size of at least 0.25 between a dose arm and placebo in the primary efficacy measure at the completion of the study was < 20%, taking into account both probability of success and tolerability if 2 or 3 arms met this criterion.

A sample size of 85 evaluable participants per non-dropped treatment arm provided approximately 80% power at a 1-sided α level of 5%, with an effect size of 0.38.

Safety was assessed in all patients who received at least 1 dose of study medication with a post-dose safety assessment (safety population).

RESULTS

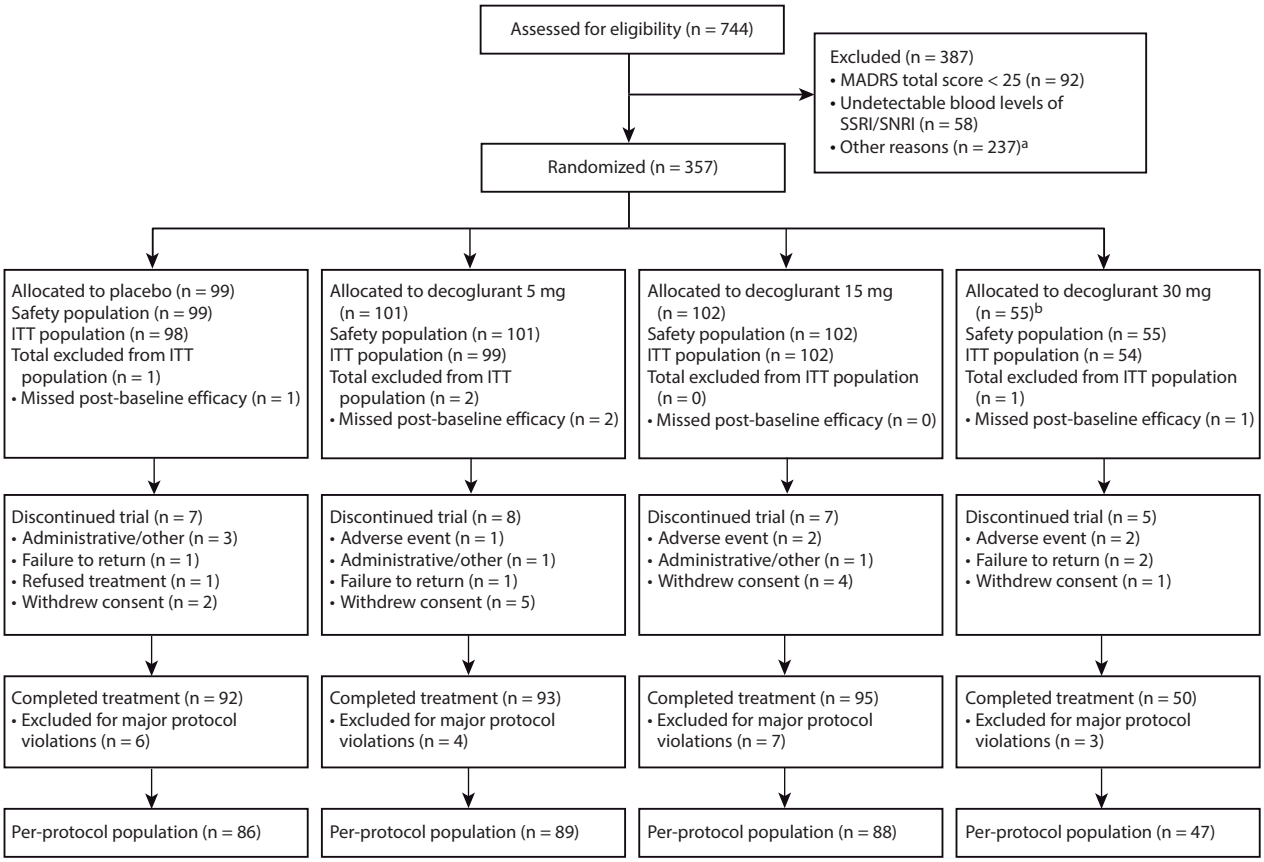
Patient Disposition and Baseline Characteristics

A total of 744 individuals were screened; among the screening failures (n = 387), 24% of patients (n = 92) were ineligible owing to MADRS scores below 25 and 15% (n = 58) for absence of detectable levels of antidepressant drug. A total of 357 patients (48% of all screened patients) passed screening and were randomized, and 310 participants completed 6 weeks of treatment without major protocol violations (Figure 1). Major protocol violations were observed in 20 patients, with similar proportions in each treatment arm. The majority of protocol violations (82%) were instances in which less than 80% (< 34) or more than 120% (> 58) of doses were received. Demographic characteristics and antidepressant treatment were well matched across arms (Table 1).

Interim Analysis

The interim analysis showed that the Bayesian predictive probabilities of reaching a final effect size of ≥ 0.25 at the end of the study were 6.5%, 3.7%, and 6.6% for decoglurant 5 mg, 15 mg, and 30 mg, respectively. The decoglurant 30-mg

Figure 1. CONSORT Trial Flow Diagram



[a]Other reasons for screening failure were as follows: exclusionary comorbid diagnoses (n = 22), positive urine illicit drug screen (n = 21), lack of documented treatment history (n = 17), current episode > 1 year in duration (n = 2), other (n = 175).
[b]Patients were initially randomized 1:1:1:1. The low number of patients in the 30-mg arm resulted from stopping recruitment to this arm after the futility analysis was conducted.
Abbreviations: ITT = intention-to-treat, MADRS = Montgomery-Åsberg Depression Rating Scale, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

arm, which was associated with the highest rate of AEs, was discontinued.

Primary Endpoint

At baseline, the mean (SD) MADRS total score across all treatment groups was 31 (6). At 6 weeks, large decreases in the MADRS total score were observed, but they did not differ significantly between decoglurant treatment and placebo groups (Figure 2, Table 2). Response and remission rates at week 6 (35%–47% and 29%–38% of patients, respectively) did not differ significantly between treatment and placebo groups (see Supplementary Figure 2 for MADRS response and remission rates). The supporting analysis using the ITT population confirmed these findings (Table 2).

No significant reductions were observed in interest-activity scores in the treatment groups compared with placebo (data not shown).

Additional analyses in subgroups of participants stratified by sex, age, history of at least 4 previous depressive episodes, a family history of MDD, baseline cognitive impairment, subjective cognitive complaints (CPFQ total score ≥ 25), and geographic region demonstrated no significant treatment effects compared with placebo.

Secondary Endpoints

Mood and functioning. Statistical analyses in both PP and ITT populations demonstrated no significant differences in secondary outcomes between decoglurant and placebo groups. Results for the IDS-SR_{30} and CPFQ are shown in Table 2 (data for other measures not shown).

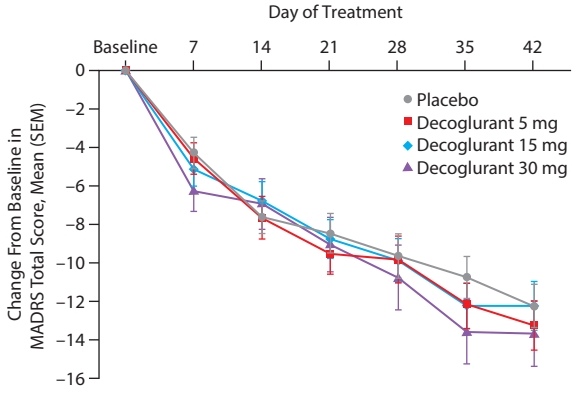
Cognitive impairment. At baseline, 24% of participants were categorized as showing cognitive impairment, while the mean cognitive performance of participants was within the normal range. At 6 weeks, none of the decoglurant doses exerted any significant effect on the CANTAB cognitive accuracy and cognitive speed composite scores compared to placebo (Table 2). Similarly, decoglurant did not significantly affect the performance of any of the individual CANTAB tasks in any arm (data not shown). Analyses in patients categorized as cognitively impaired at baseline, and in patients with a performance score of ≤ 85% on the DMS task of CANTAB (as an alternative post hoc definition

Table 1. Baseline Characteristics[a]

Characteristic	Placebo (n = 86)	Decoglurant 5 mg (n = 89)	Decoglurant 15 mg (n = 88)	Decoglurant 30 mg (n = 47)
Age, mean (SD), y	46 (11.2)	46.9 (10.7)	46.9 (10.9)	44.5 (13.1)
Age group				
≤ 45 y	46 (53.5)	35 (39.3)	35 (39.8)	22 (46.8)
> 45 y	40 (46.5)	54 (60.7)	53 (60.2)	25 (53.2)
Sex				
Male	27 (31.4)	27 (30.3)	25 (28.4)	17 (36.2)
Female	59 (68.6)	62 (69.7)	63 (71.6)	30 (63.8)
Cognitive impairment[b]				
1 (< 1 SD below normal mean)	7 (8.1)	7 (7.9)	9 (10.2)	6 (12.8)
2 (≥ 1 SD to < 0.5 SD below normal mean)	13 (15.1)	11 (12.4)	17 (19.3)	5 (10.6)
3 (> 0.5 SD below normal mean)	66 (76.7)	71 (79.8)	62 (70.5)	36 (76.6)
Years of education, mean (SD)	14.15 (2.67)	13.76 (2.44)	14 (2.31)	14.36 (2.95)
Region				
North America	51 (59.3)	55 (61.8)	54 (61.4)	29 (61.7)
Rest of world	35 (40.7)	34 (38.2)	34 (38.6)	18 (38.3)
Family history of MDD				
No	47 (54.7)	48 (53.9)	51 (58.0)	27 (57.4)
Yes	37 (43.0)	41 (46.1)	37 (42.0)	27 (57.4)
Missing	2 (2.3)	…	…	20 (42.6)
Previous depressive episodes				
≤ 4	43 (50.0)	52 (58.4)	55 (62.5)	26 (55.3)
> 4	41 (47.7)	37 (41.6)	33 (37.5)	20 (42.6)
Unknown	2 (2.3)	…	…	1 (2.1)
At least 1 SSRI treatment[c]	75 (75.8)	69 (68.3)	87 (85.3)	41 (74.5)
At least 1 SNRI treatment[c]	24 (24.2)	32 (31.7)	14 (13.7)	13 (23.6)

[a]Values shown as n (%) unless otherwise noted.
[b]Defined as follows: for < 1 SD below normative mean: 1 = impaired, 2 and 3 = nonimpaired; for < 0.5 SD below normative mean: 1 and 2 = impaired, 3 = nonimpaired.
[c]Safety analysis population: total n = 99, 101, 102, and 55, respectively.
Abbreviations: MDD = major depressive disorder, SD = standard deviation, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

Figure 2. Mean Change From Baseline in MADRS Total Score During Treatment With Placebo or Decoglurant 5, 15, or 30 mg (Per-Protocol Population)



Abbreviation: MADRS = Montgomery-Åsberg Depression Rating Scale.

of cognitive impairment), showed no significant treatment effects compared with placebo (data not shown).

Centralized Versus Site Raters

Mean changes from baseline in MADRS score as assessed by the centralized raters tended to be smaller than those assessed by site raters, particularly in the placebo group (see Supplementary Table 5 for mean changes from baseline). Response rates were higher based on site assessments, particularly in the placebo group. However, remission rates in the placebo group as assessed by centralized and site raters were comparable (Supplementary Table 5).

Pharmacokinetics and Exposure to Treatment

At 6 weeks, the mean (range) maximum plasma concentration was 143 (1–697) ng/mL with decoglurant 5 mg, 532 (1–2,090) ng/mL with 15 mg, and 835 (8–2,960) ng/mL with 30 mg; exposure thus exceeded the putative minimum therapeutic exposure of 90–100 ng/mL in all arms. Participants were grouped by their mean pre-dose plasma drug concentrations measured weekly during the last 3 weeks of treatment: < 100 ng/mL; ≥ 100–< 200 ng/mL; ≥ 200–< 300 ng/mL; and ≥ 300 ng/mL. No significant effects between exposure group and the primary and secondary endpoints were observed (data not shown). Most participants (85.5%–87.1%) in the 3 treatment arms were treated with decoglurant for > 35 days. The median (range) total dose was 210 (30–220) mg in the 5-mg arm, 630 (60–660) mg in the 15-mg arm, and 1,260 (30–1,320) mg in the 30-mg arm.

Safety

There was a low incidence of trial discontinuation due to AEs (Figure 1). The incidence of any AEs was higher in the decoglurant 30-mg treatment arm (85.5%) compared with the 5-mg (75.2%) and 15-mg (77.5%) treatment arms. The most frequent AEs included headache, nausea, and dizziness (Table 3). No deaths occurred during the trial, and few patients reported serious AEs (Table 3).

DISCUSSION

This phase 2 clinical trial investigated putative antidepressant and procognitive effects of the $mGlu_{2/3}$ antagonist decoglurant compared with placebo in individuals with partially treatment-resistant MDD. As an adjunct to SRRI/SNRI therapy, decoglurant did not demonstrate significant antidepressant or procognitive effects versus placebo and was well tolerated overall.

Drug exposure was adequate in all arms and exceeded the IC_{80} (90–100 ng/mL). No relationship between mean plasma decoglurant concentration and any main endpoint was observed. In the absence of data confirming target engagement/receptor occupancy in humans, it cannot be ruled out that central exposure to the drug was suboptimal. However, given the high brain penetrance observed in preclinical studies and the central nervous system

Table 2. Change in Primary and Secondary Endpoints From Baseline to 6 Weeks (Per-Protocol Population Except Where Noted)

Measure	Total n	Baseline Score, Mean (SD)	Mean Change From Baseline	Estimated Difference for Decoglurant – Placebo, Mean (95% CI)	Effect Size[a]	*P* Value
MADRS						
Placebo	86	30.9 (5.9)	−11.77	…	…	…
Decoglurant 5 mg	89	30.5 (5.8)	−12.82	−1.05 (−4.38 to 2.27)	0.09	.53
Decoglurant 15 mg	88	30.9 (5.7)	−11.79	−0.02 (−3.34 to 3.30)	0	.99
Decoglurant 30 mg	47	31.2 (7.4)	−13.20	−1.44 (−5.42 to 2.55)	0.13	.48
MADRS (ITT population)						
Placebo	95	31.1 (5.9)	−11.43	…	…	…
Decoglurant 5 mg	95	30.7 (5.7)	−12.04	−0.60 (−3.70 to 2.49)	0.05	.70
Decoglurant 15 mg	100	30.4 (6.3)	−10.92	0.51 (−2.54 to 3.55)	−0.05	.74
Decoglurant 30 mg	52	31.4 (7.3)	−12.12	−0.69 (−4.31 to 2.94)	0.06	.71
IDS-SR_{30}						
Placebo	86	42.7 (10.7)	−18.39	…	…	…
Decoglurant 5 mg	89	41.8 (10.3)	−18.80	−0.41 (−4.40 to 3.58)	0.03	.84
Decoglurant 15 mg	88	42.6 (9.8)	−17.96	0.43 (−3.58 to 4.43)	−0.03	.83
Decoglurant 30 mg	47	40.9 (9.6)	−17.62	0.77 (−4.02 to 5.57)	−0.06	.75
CPFQ						
Placebo	86	29.4 (5.8)	−6.00	…	…	…
Decoglurant 5 mg	89	29.1 (6.2)	−6.29	−0.29 (−0.13 to 1.55)	0.05	.76
Decoglurant 15 mg	87	30 (5)	−6.89	−0.89 (−2.75 to 0.97)	0.14	.35
Decoglurant 30 mg	46	28.1 (5.9)	−5.93	0.07 (−2.17 to 2.30)	−0.01	.95
CANTAB cognitive accuracy[b]						
Placebo	75	0.14	0.07	…	…	…
Decoglurant 5 mg	74	−0.05	0.08	0 (−0.11 to 0.11)	0.01	.95
Decoglurant 15 mg	72	0.05	0.14	0.07 (−0.04 to 0.18)	0.21	.21
Decoglurant 30 mg	35	0.09	0.04	−0.03 (−0.16 to 0.11)	−0.09	.67
CANTAB cognitive speed[b]						
Placebo	75	−0.04	0.15	…	…	…
Decoglurant 5 mg	74	−0.04	0.12	−0.03 (−0.16 to 0.11)	−0.06	.70
Decoglurant 15 mg	72	0.01	0.15	0 (−0.13 to 0.14)	0	.98
Decoglurant 30 mg	35	0.25	0.03	−0.12 (−0.29 to 0.05)	−0.3	.16

[a]Effect size was calculated as the estimated difference divided by the standard deviation. Signs have been inverted so that a positive treatment effect is reflected by a positive effect size.
[b]See Supplementary Table 4 for calculation of the CANTAB cognitive accuracy and speed scores.
Abbreviations: CANTAB = Cambridge Neuropsychological Test Automated Battery, CPFQ = Cognitive and Physical Functioning Questionnaire, IDS-SR_{30} = Inventory of Depressive Symptomatology Self Report–30-item version, ITT = intention-to-treat, MADRS = Montgomery-Åsberg Depression Rating Scale, SD = standard deviation (centralized ratings).

Table 3. Adverse Events[a]

		Decoglurant		
Adverse Event	Placebo (n = 99)	5 mg (n = 101)	15 mg (n = 102)	30 mg (n = 55)
Total	74 (74.7)	76 (75.2)	79 (77.5)	47 (85.5)
At weeks 0 to 1	30 (30.3)	39 (38.6)	46 (45.1)	33 (60.0)
Severe	7 (7.1)	7 (6.9)	6 (5.9)	6 (10.9)
Serious	1 (1)	3 (3)	2 (2.0)	0
Related				
Possible	37 (37.4)	28 (27.7)	41 (40.2)	23 (41.8)
Probable	11 (11.1)	20 (19.8)	22 (21.6)	14 (25.5)
Nervous system				
Headache	28 (28.3)	24 (23.8)	32 (31.4)	18 (32.7)
Dizziness	12 (12.1)	12 (11.9)	22 (21.6)	22 (40.0)
Somnolence	1 (1.0)	7 (6.9)	4 (3.9)	1 (1.8)
Gastrointestinal				
Nausea	15 (15.2)	10 (9.9)	25 (24.5)	16 (29.1)
Diarrhea	10 (10.1)	11 (10.9)	6 (5.9)	7 (12.1)
Vomiting	5 (5.1)	6 (5.9)	10 (9.8)	10 (18.2)

[a]All values are shown as n (%). Multiple occurrences of the same adverse event in an individual are counted only once.

nature of adverse effects observed in the safety studies in healthy volunteers, suboptimal exposure is highly unlikely.

No significant improvement in performance on the CANTAB cognitive battery was observed with decoglurant. However, the power of the study to detect a treatment effect was limited because of the lower-than-expected prevalence of clinically relevant cognitive impairment. As the primary goal of this study was to demonstrate antidepressant effects, no cognitive impairment threshold was defined as an inclusion criterion. Rather, patients were stratified into those with and those without cognitive impairment. The criterion for cognitive impairment was initially defined as 1 SD below CANTAB normative means, which was reduced to 0.5 SD because of the low number of patients meeting this initial threshold. The unexpected absence of significant cognitive impairment may have arisen because studies reporting clinically relevant cognitive impairment in MDD were performed primarily at academic centers; hence, they may have recruited from different patient populations than commercially oriented research centers. However, the absence of cognitive impairment may have been spurious and resulting from the use of normative data obtained in a restricted population, namely UK residents. Indeed, during this trial, we obtained cognitive data in age-, sex-, and education-matched controls at selected study centers in each country. Compared with these healthy volunteers, our patients were more impaired.

Lastly, the cognitive battery used may not have been optimal to detect procognitive effects of our compound—a

hypothesis that cannot be evaluated with this study alone. To detect treatment effects, future clinical trials may need to utilize an explicit cognitive impairment criterion and more than one cognitive battery, along with analyzing cognitive impairment as a primary endpoint.

Clinical trials of antidepressants in MDD have been confounded by high placebo response rates,[33–37] although data from large US Food and Drug Administration trials suggest the effect may be less than originally reported.[38] To minimize the placebo response, the current trial implemented inclusion criteria (at least moderate MADRS scores and evidence of compliance with the relevant SSRI/SNRI) and also—given the tendency for inflated site-based scoring[39]—used fully blinded, centralized raters to assess baseline severity and outcome.[37] Notably, among the individuals screened, 39% (150 patients) failed these screening criteria because of low MADRS scores or negative blood tests for SSRIs/SNRIs. Despite these initial safeguards, the placebo response and remission rates observed were high relative to previous antidepressant trials: 35% of the placebo group met the MADRS criteria for treatment response, and 29% met the MADRS criteria for full remission of MDD. These results suggest that initial patient selection may be a factor determining placebo response more strongly than outcome assessments performed by raters blinded to the protocol and study visit. We recognize that while the severity of MDD was assessed centrally in our trial, the original diagnosis of MDD was made at the individual sites. Around 15% of patients recruited to trials of MDD and resistant disease may actually be ineligible, mainly on the grounds of inadequate treatment resistance, distorting treatment effects.[40] This finding appears to be more pronounced with recruitment at non-academic, as opposed to academic, centers. As we selected patients in whom the duration of the current episode did not exceed 1 year, it can be argued that this selection criterion excluded truly treatment-resistant patients; indeed, the reasoning behind this criterion was to exclude patients in whom the likelihood of any response was expected to be very low. However, our results suggest that the patients entering our study showed, if anything, a very high response to any intervention. Other possible reasons for the high placebo response in our trial include the number of study treatment arms (leading to a probability of only 25% for a patient to be randomized to placebo)[37,41] and extended interaction with patients,[36,42] both of which have been shown to be positively associated with this effect. The challenge in first-in-patient studies is the selection of the optimal dose. Without any data on target engagement, as in the case of decoglurant, a design with only one active arm is risky, and the researcher is therefore left with a design that may increase placebo response.

Comparison of the placebo response rate to rates in studies with additional safeguards for patient selection suggests that improvements might be achieved by blinded, independent diagnosis of treatment-resistant MDD and assessment of the appropriateness of adjunctive treatment to SSRI/SNRI therapy as well as prospective testing of treatment nonresponse to background therapy before administration of study drug.[40,43–45] A double- or single-blind placebo run-in period may also be beneficial.[36] Nonetheless, while it is clear that the aforementioned improvements should be implemented for future trials, the absence of any signal of a treatment effect in our study across multiple endpoints in the subgroup analyses supports our conclusion that decoglurant does not exert any antidepressant effects.

To conclude, decoglurant was well tolerated, and, at the doses investigated, no antidepressant or procognitive effects were observed in individuals with partially treatment-resistant MDD compared with placebo. A relatively high placebo response and a seeming absence of clinically relevant cognitive impairment in the majority of patients may have reduced the possibility of demonstrating antidepressant and procognitive effects. An even more careful selection of patients may help to address these issues in future trials.

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Additional information: All reasonable requests for access to study data will be facilitated whenever possible and should be directed to the corresponding author.

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Supplementary Material

Article Title: Randomized, Double-Blind, Placebo-Controlled Trial of the $mGlu_{2/3}$ Negative Allosteric Modulator Decoglurant in Partially Refractory Major Depressive Disorder

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List of Supplementary Material for the article

1. **Table 1** Inclusion and exclusion criteria
2. **Table 2** Administration of study medication
3. **Table 3** Exploratory factor analysis
4. **Table 4** Cambridge Neuropsychological Test Automated Battery (CANTAB) tasks and composite score computation
5. **Table 5** Mean changes from baseline to day 42 in MADRS score, and response and remission rates, as assessed by the centralized and site raters
6. **Figure 1** Trial design and schedule of endpoint assessments
7. **Figure 2** MADRS response and remission rates. (a) Response rates, defined as MADRS reduction of ≥50%; (b) Remission rates, defined as total MADRS score ≤10. *P*-values are from Fisher exact test results at day 42

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Supplementary Table 1. Inclusion and exclusion criteria

Inclusion criteria
1. An outpatient with a primary diagnosis of MDD without psychotic features as defined by DSM-IV-TR, on the basis of a structured interview (Structured Clinical Interview for DSM-IV-TR clinical trial version [SCID-CT]).
2. Having inadequate response to current, ongoing antidepressant treatment including an SSRI/SNRI. Inadequate response is defined as having a CGI-S score ≥4 (moderately ill or worse) and an MADRS score ≥25 (generated at screening) while being treated for at least 6 weeks at a dose equal to or greater than the minimum acceptable dose indicated in the MGH ATRQ.
3. Having at least one but no more than two antidepressant treatment trial failures within the index depressive episode, with the current, ongoing antidepressant trial counted as one treatment failure. A single antidepressant treatment regimen including more than one pharmacological agent (eg, combination or augmentation) will only be considered as a single antidepressant trial.
4. Dose and duration of antidepressant treatment in the index episode can be verified by written documentation from at least one of the following: medical records; pharmacy records; treating and/or referring physician (indicating medication, dose, and dates of treatment).
5. Documentation of clinical and treatment history must be available.
6. The index depressive episode should have started within 1 year of screening.
7. Confirmed compliance with current SSRI/SNRI treatment based on blood screen.
8. Existing medication regimens should be stable for 6 weeks, with the intent to remain stable throughout the study.
9. Legally adult (minimum of 18 up to 65 years of age at time of informed consent).
10. BMI 18.0–35.0 kg/m^2 inclusive.
11. Patients with reproductive potential must agree to use contraceptive protection from screening until 90 days after the last dose of study medication as follows: - Males with partners of childbearing potential or partners must use a barrier method of contraception or remain sexually abstinent. - Females who are not either surgically sterile (tubal ligation, removal of ovaries or uterus) or post-menopausal (no spontaneous menstrual periods for at least 1 year confirmed by a hormone panel [FSH and 17βestradiol]) must agree to use two adequate methods of contraception, including at least one method with a failure rate of <1% per year (eg, hormonal implants, combined oral contraceptives, vasectomized partner, abstinence).
12. In the investigator's opinion, the patient is deemed appropriate for participation in the study, capable of following the study schedule of assessments and complying with the

study restrictions and participation in the study, or discontinuation of prohibited medication will not pose undue risks to the patient.
13. Able to participate and willing to give written informed consent.
Exclusion criteria
1. Currently receiving treatment with a combination of three or more antidepressants.
2. Currently receiving treatment with prohibited medications (see list at end of table) and not willing to cease treatment at least 2 weeks before randomization (or 5 half-lives, whichever is longer).
3. Significant ongoing use of high doses of barbiturates, benzodiazepines or other anxiolytic drugs, withdrawal from which is judged by the investigator to be clinically inadvisable.
4. Previously received decoglurant.
5. Participated in an investigational drug or device study within 6 months of screening or in the index depressive episode.
6. History of non-response to, or current use of, a non-pharmacological treatment including electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), or repetitive transcranial magnetic stimulation (RTMS).
7. Planning to begin or change current regimen of individual psychotherapy, including cognitive behavioral therapy, during the 6-week treatment period of the study and the first 2 weeks of follow-up. Patients undergoing regular psychotherapy (ie, at least 3 months' duration at the time of screening) are eligible to participate in the study.
8. Present DSM-IV-TR axis I diagnosis, except for anxiety comorbidity (obsessive compulsive disorder or post-traumatic stress disorder specifically not allowed).
9. Past or present psychotic symptoms.
10. Mood disorder owing to a medical condition or substance use/abuse/dependence.
11. Established personality disorder that might interfere with compliance or increase suicidal risk.
12. Alcohol and/or substance abuse/dependence during the last 6 months.
13. A current (at screening) significant risk for suicidal behavior as judged by the investigator following a thorough clinical evaluation and supported by information collected on the C-SSRS.
14. Past or present neurological disorder (for example, but not restricted to, seizure disorder, stroke, head trauma, disorders associated with ataxia or vertigo, dementia or neurodegenerative disorders).

15. Present eating disorder (anorexia nervosa and bulimia nervosa).
16. Abnormal thyroid function. Note that patients undergoing treatment may be allowed to participate in the study if currently euthyroid and not having had a change in treatment regimen within the last 8 weeks.
17. Active upper gastrointestinal tract disease (stomach ulcer/peptic ulcer, gastritis/gastroenteritis or GERD).
18. Other significant or unstable medical condition that could interfere with, or for which the treatment of might interfere with, the conduct of the study, or that would, in the opinion of the investigator, pose an unacceptable risk to the patient in this study.
19. Positive result on hepatitis B (HBV), hepatitis C (HCV), or HIV 1 and 2.
20. Positive test for abuse of drugs.
21. Clinically significant abnormality on 12-lead electrocardiogram (ECG), including a QTcF of ≥450 milliseconds.
22. Clinically significant lab abnormality (note that re-testing is allowed to rule out potential laboratory errors).
23. For females of child-bearing potential, positive pregnancy test, breast-feeding, or intention to become pregnant during the course of the trial.
24. Hypersensitivity to the excipients of the study drug.
25. Individuals whose occupation is to drive or operate mass transportation (ie, buses, trains), large vehicles (ie, trucks), or heavy machinery.
Prohibited medications
The following medications were prohibited at least 2 weeks or up to 5 half-lives (whichever was longer) before randomization until the end of the 8-week follow-up period: – Strong CYP1A inhibitors (eg, fluvoxamine, ciprofloxacin) – Strong CYP450 enzyme inducers (eg, rifampicin, EIAEDs [eg, carbamazepine, phenytoin], St John's Wort) – Substrates for PgP with a narrow therapeutic window (eg, digoxin) – Other drugs with a narrow therapeutic window (eg, theophylline, warfarin)

The following medications were prohibited at least 2 weeks or up to 5 half-lives (whichever was longer) before randomization until after at least 2 weeks of follow-up. (Note that use of these agents before the end of the 8-week follow-up period was only permitted following consultation with the Sponsor/Medical Monitor).

- Non-SSRI or non-SNRI antidepressants (eg, moclobemide, clomipramine, trazodone)
- Second antidepressant if patient was on two antidepressants at screening
- Alternative therapies/herbal supplements used as antidepressants (eg, omega-3 fatty acids)
- Adjunctive or potentiating antidepressant treatments (eg, antipsychotics [typical or atypical], mood stabilizers, lithium, triiodothyronine or stimulants)
- Opioid analgesics (eg, tramadol)
- GABA agonists (eg, tiagabine, vigabatrin, baclofen)
- Glutamatergic drugs (eg, riluzole, topiramate, memantine, lamotrigine)
- MAO inhibitors
- 5-hydroxytryptophan L-tryptophan
- All other psychotropic drugs (with the exception of allowed medications listed above)

BMI, body mass index; CGI-S, Clinical Global Impression – Severity; C-SSRS, Columbia Suicide Severity Rating Scale; CYP, cytochrome P; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision; EIAEDs, enzyme-inducing antiepileptic drugs; FSH, follicle-stimulating hormone; GABA, gamma-aminobutyric acid; GERD, gastroesophageal reflux disease; HIV, human immunodeficiency virus; MADRS, Montgomery–Åsberg Depression Rating Scale; MAO, monoamine oxidase; MDD, major depressive disorder; MGH ATRQ, Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; QTcF, QT interval corrected for heart rate via Fridericia's method; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

Supplementary Table 2. Administration of study medication

The first dose of study medication (decoglurant 5 mg, 15 mg, or 30 mg or placebo) was administered in the clinic on day 1 within 15 minutes of completing a meal. Patients remained at the clinic for at least 4 hours after the first dose for safety monitoring and other assessments.
On clinic visit days involving pharmacokinetic (PK) sampling, patients arrived at the clinic in the morning without having taken their daily dose of study medication. Following collection of the pre-dose PK blood sample and within 15 minutes of completing a meal, patients took their dose of study medication.
On clinic visit days not involving PK sampling, patients took their daily dose of study medication in the morning, either before or after arrival at the clinic and within 15 minutes of completing a meal.
On days when a study visit was not scheduled, patients took their dose once daily in the morning within 15 minutes of completing a meal.
The last dose of study medication was administered on day 42 (+/− 2 days).
Patients were required to complete a daily diary to record the actual time of dosing. The actual time of the first meal consumed on each day of the treatment period and the meal consumed on the evening before clinic visits were also recorded in the patient diary, as well as information regarding skipped doses and vomiting.

Supplementary Table 3. Exploratory factor analysis

Rotated factor pattern				
	Study NP25620 (*N* = 181)		**Study BP25712 (*N* = 115)**	
	Factor 1	**Factor 2**	**Factor 1**	**Factor 2**
OTS – Problems solved on first choice	73	12	62	–14
RVP – A prime	72	–40	78	–14
DMS – Percent correct	52	–32	49	–20
PAL – Total errors (adjusted)	–69	8	–65	15
AST – Incongruent errors	–75	–1	–81	–22
AST – Reaction latency (median, congruent)	–23	73	–19	76
DMS – Correct latency, mean	3	72	15	73
RVP – Median response latency	–38	69	–56	50
OTS – Median correct latency	7	52	–26	49

Printed values are multiplied by 100. AST, attentional set shifting; DMS, delayed matching to sample; N, number of patients; OTS, One-Touch Stockings of Cambridge; PAL, paired associates learning; RVP, rapid visual processing.

Supplementary Table 4. Cambridge Neuropsychological Test Automated Battery (CANTAB) tasks and composite score computation

Task	Abbreviation for test	Domain	Key parameter	Abbreviation for scores
Attentional set shifting	AST	Attention; executive function	Incongruent errors Reaction latency (median, congruent)	ASTICE ASTLCMD
Delayed matching to sample	DMS	Working memory	Percent correct overall Correct latency (mean)	DMSPC DMSML
One-Touch Stockings of Cambridge	OTS	Executive Function	Problems solved on first choice Correct latency (median)	OTSPSFC OTSMDCL
Paired associates learning	PAL	Episodic memory	Total errors (adjusted)	PALTEA
Rapid visual processing	RVP	Attention	A prime Median response latency	RVPA RVPMDL
Accuracy composite score	= (DMSPC*+OTSPSFC*−PALTEA*+RVPA*−ASTICE*)/5, where DMSPC*, OTSPSFC*, PALTEA*, RVPA*, ASTICE* are the standardized values of the original variables			
Speed composite score	= −1*(DMSML*+RVPMDL*+ASTLCMD*+OTSMDCL*)/4, where DMSML*, RVPMDL*, ASTLCMD*, OTSMDCL* are the standardized values of the original variables			

Supplementary Table 5. Mean changes from baseline to day 42 in MADRS score, and response and remission rates, as assessed by the centralized and site raters

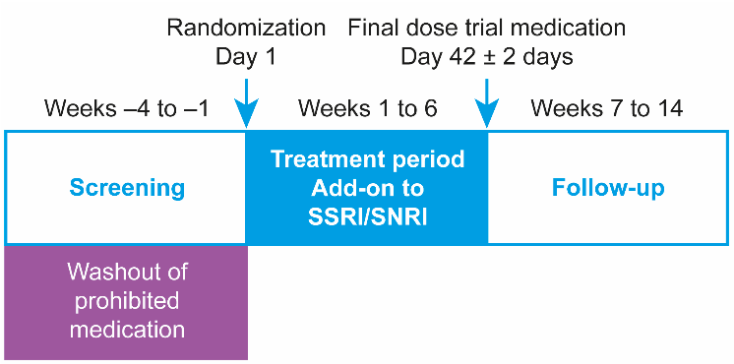
	Placebo		**Decoglurant 5 mg**		**Decoglurant 15 mg**		**Decoglurant 30 mg**	
	***n* = 86**		***n* = 89**		***n* = 88**		***n* = 47**	
	Centralized	**Site**	**Centralized**	**Site**	**Centralized**	**Site**	**Centralized**	**Site**
Change in MADRS total score[a]								
Mean (SD)	−11.8 (11.2)	−14.5 (10.1)	−12.8 (11.2)	−15.0 (10.1)	−11.8 (11.2)	−13.7 (10.1)	−13.2 (11.2)	−13.2 (10.1)
95% CI	[−14.2, −9.4]	[−16.7, −12.3]	[−15.2, −10.5]	[−17.2, −12.8]	[−14.2, −9.4]	[−15.9, −11.5]	[−16.4, −10.0]	[−16.1, −10.2]
Response at day 42, %[b]	34.9	47.7	39.3	47.2	43.2	51.1	46.8	46.8
Remission at day 42, %[b]	29.1	30.2	37.1	38.2	29.5	37.5	31.9	29.8

[a]Change from baseline, least-squares means from mixed-model repeated measures.

[b]Response defined as MADRS reduction of ≥50%, remission defined as total MADRS score ≤10.

CI, confidence interval; MADRS, Montgomery–Åsberg Depression Rating Scale; SD, standard deviation.

Supplementary Figure 1. Trial design and schedule of endpoint assessments

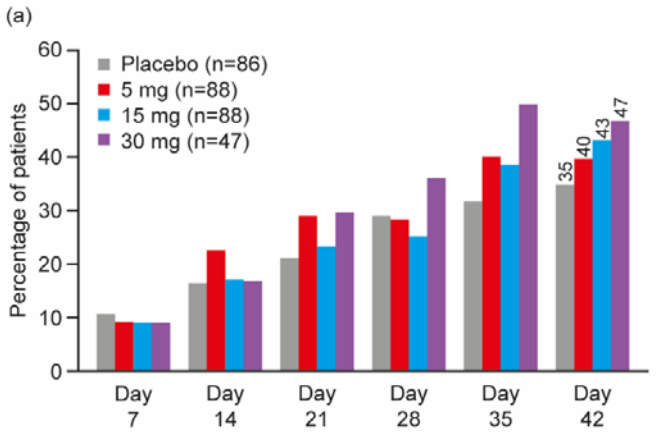


Schedule of endpoint assessments

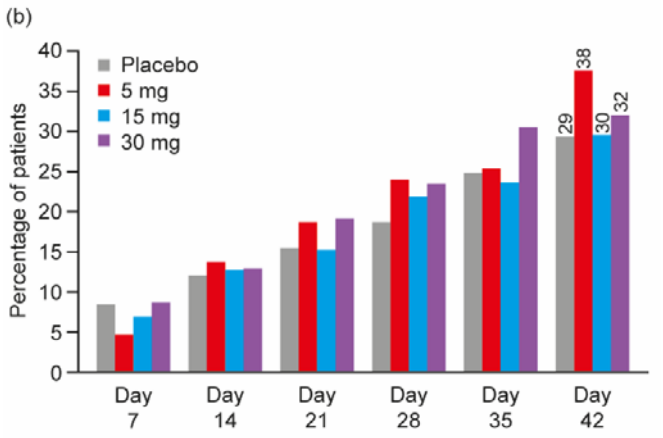
Scale	Screening	Baseline		W1	W2	W3	W4	W5	W6		W8	W10	W14
MADRS	CR	Site	CR	CR	CR	CR	CR	CR	Site	CR	CR	CR	CR
CGI-S	CR	Site	CR	CR	CR	CR	CR	CR	Site	CR	CR	CR	CR
CANTAB	Pt	Pt		Pt					Pt				
CGI-I									Site				
IDS-SR30	Pt	Pt		Pt	Pt	Pt	Pt	Pt	Pt		Pt	Pt	Pt
PGI				Pt	Pt	Pt	Pt	Pt	Pt				Pt
CPFQ		Pt							Pt				Pt
SDS		Pt		Pt	Pt	Pt	Pt	Pt	Pt		Pt	Pt	Pt
Q-LES-Q-SF		Pt							Pt				Pt

CANTAB, Cambridge Neuropsychological Test Automated Battery; CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinical Global Impression – Severity of Illness scale; CPFQ, Cognitive and Physical Functioning Questionnaire; CR, centralized rater; IDS-SR30, Inventory of Depressive Symptomatology Self Report-30 item version; MADRS, Montgomery–Åsberg Depression Rating Scale; PGI, Patient-Rated Global Improvement; Pt, patient; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form; SDS, Sheehan Disability Scale; W, week.

Supplementary Figure 2. MADRS response and remission rates. (a) Response rates, defined as MADRS reduction of ≥50%; (b) Remission rates, defined as total MADRS score ≤10. *P*-values are from Fisher exact test results at day 42



	Decog 5 mg	Decog 15 mg	Decog 30 mg
Unadjusted *P*-value (Fisher exact test results: Decog vs. placebo)	0.64	0.28	0.20



	Decog 5 mg	Decog 15 mg	Decog 30 mg
Unadjusted *P*-value (Fisher exact test results: Decog vs. placebo)	0.27	1.00	0.84

Decog, decoglurant.