Original Investigation

Efficacy and Safety of Basimglurant as Adjunctive Therapy for Major Depression
A Randomized Clinical Trial

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IMPORTANCE Antagonism of the postsynaptic metabotropic glutamate subtype 5 receptor is a novel approach to modulate glutamatergic function and has proven efficacy in a number of preclinical behavioral models of depression.

OBJECTIVE To evaluate the safety and efficacy of basimglurant modified-release (MR) vs placebo as adjunctive therapy to ongoing antidepressant medication therapy in patients with MDD who had inadequate response within the current episode.

DESIGN, SETTING, AND PARTICIPANTS In this phase 2b, double blind, randomized clinical trial of 333 adult patients with a *DSM-IV-TR* diagnosis of MDD across 59 research clinics globally, patients were assigned to 1 of 2 doses of basimglurant MR (0.5 or 1.5 mg) or placebo once daily, adjunctive to ongoing antidepressant medication therapy (selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor). Patients were enrolled from October 5, 2011, through July 26, 2013.

INTERVENTIONS Six-week treatment with 0.5 mg of basimglurant MR, 1.5-mg basimglurant MR, or placebo once daily, adjunctive to ongoing antidepressant medication therapy.

MAIN OUTCOMES AND MEASURES The primary end point was the mean change from baseline score on the Montgomery-Åsberg Depression Rating Scale (MADRS), as rated by the clinician at week 6. Other measures included patient-rated MADRS, Quick Inventory of Depressive Symptomatology–Self-Report, Clinical Global Impression–Improvement, Patient Global Impression–Improvement, and Clinical Global Impression–Severity Scales and adverse events.

RESULTS A total of 596 patients were screened, and 333 were randomized into the study (mean [SD] age, 47 [11.2] years; 216 female [65.1%]). The primary end point (mean change in clinician-rated MADRS score from baseline to end of treatment) was not met (effect size [ES] = 0.16, P = .42; intent-to-treat [ITT] mixed-effects model for repeated measures [MMRM] analysis for comparing 1.5-mg basimglurant MR and placebo). Across secondary and exploratory end points, 1.5-mg basimglurant MR revealed larger improvements vs placebo on the patient-rated MADRS (−16.2 vs −13.3, ES = 0.28, nominal P = .04), Quick Inventory of Depressive Symptomatology–Self-Report (−7.5 vs −5.8; ES = 0.37, nominal P = .009), Clinical Global Impression–Improvement mean score, and Patient Global Impression–Improvement mean score. Improvements were also seen in the patient-rated MADRS remission rate (36.0% vs 22.0%; nominal P = .03) and response rate (50.5% vs 40.4%; nominal P = .13), A 0.5-mg dose of basimglurant MR had no benefit over placebo in any of these measures. The most common adverse event was dizziness, which was mostly transient and of mild intensity.

CONCLUSIONS AND RELEVANCE No difference was observed on the study's primary outcome measure, the clinician-rated MADRS change from baseline to end of treatment, between adjunctive basimglurant MR vs placebo. Adjunctive 1.5-mg basimglurant MR daily revealed, however, an antidepressant effect across secondary end points, particularly in patient-rated measures. These findings combined with good tolerability warrant further investigation with this compound in depressive disorders.

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Major depressive disorder (MDD) remains an area of considerable medical need despite many agents having been approved for treatment of this illness. Response rates (reduction in symptoms of at least 50% from baseline) for initial treatment are estimated to be approximately 50%, whereas remission (the virtual absence of symptoms), considered to be the goal of treatment, only ranges from 15% up to 40%.[1] The results of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial have provided sobering conclusions regarding the efficacy of approved antidepressant treatments, with only one-third of patients achieving remission with initial therapy, and remission decreasing even further with each successive treatment attempt (36.8% after the first attempt, 30.6% after the second attempt, 13.7% after the third attempt, and 13.0% after the fourth attempt).[2] Moreover, various switching strategies used as second-line treatment did not yield very different results.[3]

Failure to obtain remission in MDD using largely monoaminergic-based pharmacotherapy, therefore, remains a common clinical problem. Persistent depressive symptoms are a significant predictor of relapse and poor functional outcome.[4-6] Patients who are resistant to treatment use a disproportionately larger share of health care resources, have significantly more claims for comorbid conditions, and have an associated higher loss of productivity compared with patients with major depression who respond to treatment. New treatments that address inadequate response to antidepressant therapy in MDD would fulfill an important medical need.

During the last decade, evidence has accumulated indicating the pathophysiologic role of deregulated cortical glutamatergic pathways in major depression, including the demonstration of abnormal levels of glutamate and altered expression of glutamate receptors in patients with depression.[7-13] Supportive evidence of the antidepressant effects of antiglutamatergic drugs stems from pilot clinical trials with ketamine, an *N*-methyl-D-aspartate (NMDA) channel-blocking agent, which have a fast-acting antidepressant effect in treatment-resistant patients.[14,15] The postsynaptic colocalization of NMDA receptors and metabotropic glutamate subtype 5 (mGlu5) receptors in cortical and limbic regions[16] and the downstream effects of mGlu5 receptor blockade down-regulating NMDA function[17] provide a strong rationale for the potential antidepressant effect of mGlu5 receptor antagonism. Given the concerns regarding the clinical use of ketamine, including psychotigenic effects and potential for addiction,[18] mGlu5-negative allosteric modulators become an even more attractive target for the development of novel antidepressants.[19]

Basimglurant is a potent, selective, and safe mGlu5-negative allosteric modulator with good oral bioavailability and long half-life supportive of once-daily administration in humans. It also possesses robust antidepressant and anxiolytic-like properties in preclinical models.[20,21] Unpublished data (clinicaltrials.gov, NCT00809562) from a placebo-controlled study[22] in inpatients with treatment-resistant depression treated for 10 days revealed that 0.1 mg to 1.5-mg basimglurant was well tolerated, with trends of clinical effects warranting further evaluation in a larger, well-powered clinical trial. A modified-release (MR) formulation was developed to improve safety and tolerability vs the immediate-release (IR) formulation used in earlier clinical studies. This MR formulation improved the pharmacokinetics by decreasing the maximum concentration by approximately 50% and prolonging the time to reach the maximum concentration to approximately 5 hours relative to the IR formulation. These differences between the MR and IR formulations did not affect the overall exposure (area under the curve). The aim of this study was to evaluate the safety and efficacy of once-daily basimglurant MR or placebo added to continuing antidepressant medication therapy in patients with MDD who had inadequate response to at least 1 but no more than 3 treatment failures within the current episode of depression.

Key Points

Question Does basimglurant modified-release (MR), a metabotropic glutamate subtype 5 receptor–negative allosteric modulator, improve outcomes in major depressive disorder when added to a current antidepressant medication treatment?

Findings In this randomized clinical trial of 333 adults with major depressive disorder, no difference was observed in the primary outcome measure, the clinician-rated Montgomery-Åsberg Depression Rating Scale change from baseline to end of treatment, between basimglurant MR (0.5 or 1.5 mg) vs placebo. However, 1.5-mg basimglurant MR had a consistent antidepressant effect across secondary end points, particularly in patient-rated measures.

Meaning These findings, combined with adequate tolerability, warrant further investigation with this compound in depressive disorders.

Methods

Study Design

This randomized, double-blind, placebo-controlled, multicenter phase 2 study (Modulating Receptors of Glutamate for Alleviating Depression [MARIGOLD]) was composed of a screening period of 2 weeks or less, a 6-week double-blind treatment, and a 3-week posttreatment follow-up period. Patients were enrolled from 59 sites across the United States, Latin America (Chile and Mexico), Europe (Germany, Poland, Russia, and Romania), and Asia (Japan) from October 5, 2011, through July 26, 2013. Data analysis was performed from November 12, 2013, to September 27, 2014. The study was conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonization, Good Clinical Practice guidelines, and local regulatory requirements. The institutional review board or ethics committee approved the protocol at each site. All patients gave written informed consent to participate in the study. An independent data safety monitoring board composed of nonsponsor members reviewed unmasked safety data at predefined intervals and made recommendations to the sponsor's chief medical officer regarding the continued conduct of the study. After randomization, study

visits occurred at days 3, 7, 14, 21, 28, 35, 42, and 63. The trial protocol can be found in the Supplement.

Patients

Male and female outpatients (age range, 18-70 years) who met the *DSM-IV-TR* criteria for an MDD episode without psychotic features were enrolled.[23] Diagnoses were made by the Mini-International Neuropsychiatric Interview (MINI)[24] and confirmed by a computer-administered diagnostic interview, which was completed by patients and reviewed via a central vendor (Bracket Global) specialized in MDD diagnosis. The computer-administered diagnostic interview is a complement to the MINI, focusing on the key dimensions of MDD to supplement the categorical diagnostic tool (the MINI). Bracket Global clinicians reviewed the data for diagnostic flags that could indicate uncertainty in the diagnosis required for participation, such as symptoms suggestive of previous hypomanic episodes, lack of treatment response, or a substance abuse component. In these cases, Bracket Global clinicians contacted sites to discuss questionable individuals in a process designed as a consultation. Patients had to have inadequate response to ongoing antidepressant therapy with a selective serotonin reuptake inhibitor or serotonin and norepinephrine reuptake inhibitor. Patients had to have 1 but no more than 3 treatment failures of adequate dose and duration (>6 weeks) according to the Massachusetts General Hospital Antidepressant Treatment History Questionnaire[25] in the current episode. Inadequate response was defined as having a clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS)[26] total score greater than 25 and a Clinical Global Impression-Severity (CGI-S)[27] score greater than 4 at screening. In addition, patients had to have a score greater than 23 on a computer-assisted, self-administered version of the MADRS (the patient-rated MADRS)[28-30] and a discrepancy of 7 points or fewer with the clinician-rated MADRS score.

Patients were excluded if having any other major Axis I diagnoses (generalized anxiety disorder secondary to depression was allowed), a lifetime history of psychotic symptoms or bipolar disorder, a significant personality disorder, a mood disorder owing to a medical condition or substance use, recent alcohol or substance abuse, or a significant risk of suicidal behavior. Other reasons for exclusion included treatment with a combination of antidepressants, having undergone electroconvulsive therapy or repetitive transcranial magnetic stimulation during the current episode or having a history of failure to these therapies, having ever used vagus nerve stimulation or deep brain stimulation, or planning to begin psychotherapy during the study (unless it had been ongoing for ≥90 days before screening). Fluvoxamine maleate was prohibited because of the theoretical potential to interact with basimglurant (via inhibition of hepatic cytochrome P450 1A2 enzymes).

Treatment

After eligibility was confirmed, patients were randomized (1:1:1 ratio) to receive 6-week double-blind treatment, adjunctive to their ongoing antidepressant medication therapy, with 0.5 mg of basimglurant MR, 1.5-mg basimglurant MR, or placebo orally and once daily (**Figure 1**). The randomization was stratified by geographic region. Treatment adherence was assessed at each visit based on the returned capsule count.

Ongoing antidepressant therapy was maintained at the same dose for the 6-week double-blind period but could have been adjusted as deemed necessary in the follow-up period. Use of other psychotropic medications was prohibited 2 weeks before randomization with the exception of preexisting stable regimens of benzodiazepines. For acute anxiety and/or insomnia, rescue medication with a benzodiazepine (≤2 mg of lorazepam equivalent) or nonbenzodiazepine (eg, ≤10 mg of zolpidem tartrate or zaleplon) was allowed on a restricted basis.

Efficacy Evaluations

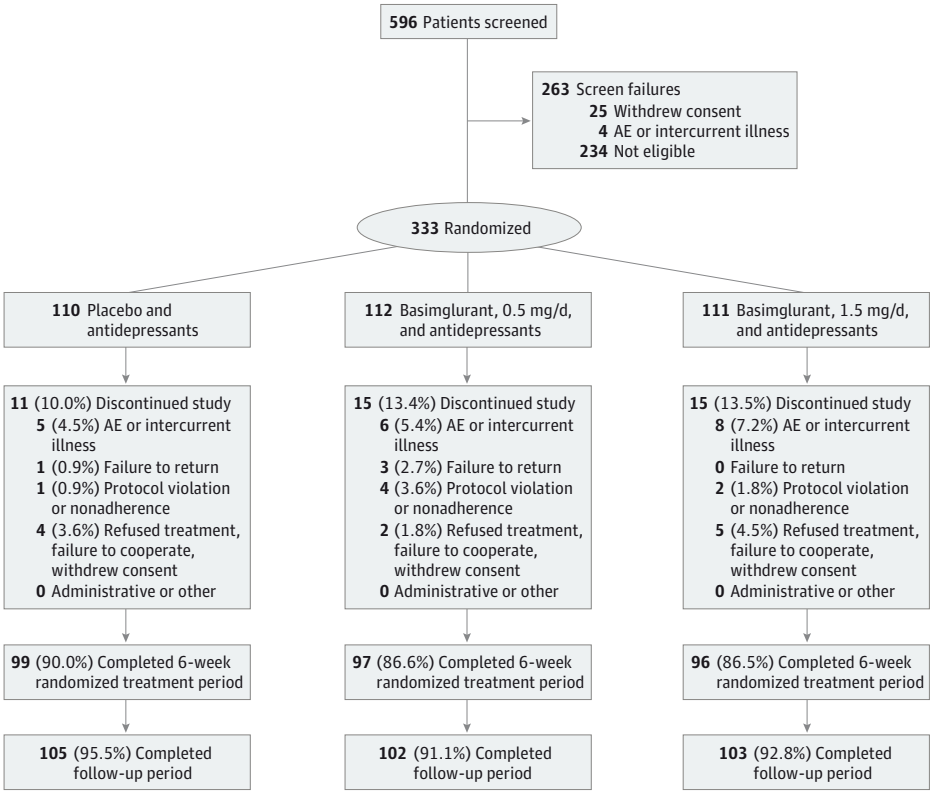
The primary end point was the mean change in the clinician-rated MADRS total score from baseline to end of treatment. Secondary end points included change in CGI-S and Clinical Global Impression–Improvement (CGI-I) scores from baseline to end of treatment, MADRS remission rates (MADRS total score ≤10) at end of treatment, MADRS response rates (≥50% reduction in MADRS total score from baseline), the 16-item Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR16)[31] change from baseline to end of treatment, and the Patient Global Impression of Improvement (PGI-I) score at end of treatment. Exploratory end points included change in Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF)[32] and Sheehan Disability Scale (SDS)[33] scores from baseline to end of treatment. The patient-rated MADRS total score change from baseline to day 42 was a post hoc analysis and not a prespecified end point.

Investigators and site raters received standardized training on all scales to ensure consistency across the study. All raters performing the clinician-rated MADRS, CGI-I, and CGI-S had to meet minimum qualification criteria and become certified to rate patients. Efforts were made to ensure the same rater conducted all assessments of a particular scale for a given patient to minimize scoring variability. In addition, a rater monitoring program was implemented for quality control purposes. Scores on the clinician- and patient-rated MADRS were continually reviewed for consistency by the ratings vendor, whose clinicians held calls with site raters to discuss sources of discordance and offer retraining when warranted. For the primary efficacy measure (clinician-rated MADRS), 226 raters were approved and certified to perform ratings.

Safety and Tolerability

Safety and tolerability assessments included the monitoring of spontaneously reported adverse events (AEs), physical examination, vital signs and body weight, and 12-lead electrocardiography performed in triplicate. Laboratory tests included measurement of hematologic, chemical, and thyroid parameters; urinalysis; urine drugs of abuse screening; and pregnancy testing. The incidence of suicidal ideation and behavior was monitored using the Columbia-

Figure 1. Flow of Patients During the Study



AE indicates adverse event.

Suicide Severity Rating Scale, interactive voice response version,[34] at each visit.

Statistical Analysis

Two patient samples were defined: an intent-to-treat (ITT) sample (all randomized patients who received at least 1 dose of the randomized study drug) and the safety sample (all patients who received at least 1 dose of the study medication, whether withdrawn prematurely or not). The ITT sample was the primary analysis sample for all analyses of primary and secondary clinical efficacy data.

For all efficacy variables, the baseline value was defined as the last nonmissing value taken before the start of the double-blind period. The primary end point and continuous secondary end points were analyzed using a mixed-effects model for repeated measures to use all the data collected over time. This method allowed a general unstructured covariance matrix and enabled inclusion of data from patients who had missing data at some scheduled time points. The model included the baseline value as covariate; the categorical variables treatment, geographic region (Europe, Latin America, Japan, and United States), and visit time point; and an interaction term of visit with treatment. Ordered categorical data (CGI-S, CGI-I, and PGI-I scores) were analyzed using the Wilcoxon rank sum test. Binary data, such as responders or remissions, were analyzed using the Fisher exact test. Unadjusted, unpaired, 2-sided *P* values were estimated. All exploratory variables and safety and tolerability were summarized descriptively.

Results

Patient Disposition and Characteristics

Figure 1 illustrates the disposition of patients during the study. A total of 596 patients were screened. The main reasons for screen failures, which totaled 263, were failure to meet inclusion criteria with regard to disease severity or MADRS score criteria not met (n = 96 patients screened) and a positive serologic test result for human immunodeficiency virus or hepatitis B or C virus (n = 49 patients screened). Of the 333 patients randomized into the study (mean [SD] age, 47 [11.2] years; 240 white patients [72.3%]; 216 female patients [65.1%]), all but 1 were included in the ITT sample (332 patients [99.7%]; same as the safety sample). This 1 patient was randomized to the placebo group but withdrew consent on study day 1 before receiving the study treatment. The treatment blind was not broken prematurely by the sponsor or investigator during the study. The proportion of patients who withdrew because of refusal of treatment (including withdrawal of consent and failure to cooperate) was similar between the placebo and 1.5-mg basimglurant MR arms (4 and 5 patients, respectively) and somewhat lower in the 0.5-mg basimglurant MR arm (2 patients). The

number of patients withdrawn for protocol violations was slightly higher in the 0.5-mg basimglurant MR arm (4 patients) compared with the placebo (1 patient) and 1.5-mg basimglurant MR arms (2 patients).

The patients' demographic characteristics were generally well matched across all 3 treatment arms (**Table 1**). All patients had a primary diagnosis of MDD, with a mean MADRS total score of approximately 31 and a mean QIDS-SR16 total score of approximately 14, corresponding to moderate to severe depression. Most patients had recurrent depression (89.0%-91.1%), with the mean number of episodes ranging from 4 to 5 across the 3 treatment arms. Within the current episode, most of the patients reported a single treatment failure (80.4%-83.5%).

The most common class of baseline antidepressant therapy was selective serotonin reuptake inhibitors (received by 74.7%-83.5% of patients). The distribution of antidepressant treatments was similar across study arms, although fewer patients received sertraline hydrochloride in the 1.5-mg basimglurant MR arm (21.6% vs 31.2%-33.0%).

Efficacy

Mean change in clinician-rated MADRS total score from baseline to day 42 (primary end point) was reduced in each treatment arm (−14.6 in the placebo arm, −14.1 in the 0.5-mg basimglurant MR arm, and −16.1 in the 1.5-mg basimglurant MR arm) (**Figure 2**). Neither active treatment arm was found to be significantly different from placebo (for the 0.5-mg arm, adjusted $P = .74$ and effect size [ES] = −0.05; for the 1.5-mg arm, adjusted $P = .42$ and ES = 0.16). The post hoc analysis of the patient-rated MADRS revealed larger differences between 1.5-mg basimglurant MR and placebo compared with the clinician-rated MADRS (−16.2 vs −13.3; 2-sided $P = .04$, ES = 0.28) (Figure 2).

The proportion of patients taking basimglurant who experienced remission (total score ≤10) or response (≥50% reduction in total score) based on the clinician-rated MADRS at day 42 was not different from placebo. However, remission and response rates based on the post hoc patient-rated MADRS in the ITT sample (last observation carried forward) were greater in the 1.5-mg basimglurant MR arm than in placebo (36.0% vs 22.0%; 2-sided $P = .03$ and 50.5% vs 40.4%; 2-sided $P = .13$, for remission and response, respectively).

For the QIDS-SR16, a decrease from baseline to day 42 (ie, improvement) was observed in the 1.5-mg basimglurant MR arm compared with placebo (−7.5 vs −5.8; 2-sided $P = .009$) (Figure 2). The decrease of 7.5 points observed for 1.5-mg basimglurant MR represented an approximately 50% reduction in score from baseline compared with the decrease of 5.8 points for placebo (approximately 40% reduction). The associated ES of 0.37 is clinically relevant.

The results for other secondary and exploratory efficacy measures are given in **Table 2**. For 1.5-mg basimglurant MR, improvements at day 42 vs placebo were seen in the CGI-I, PGI-I, Q-LES-Q-SF, and SDS (sum of items 2-3). The SDS total scores could not be calculated for all patients because a significant proportion of them (25.2%-34.9%) were not working for reasons other than depression (and did not score item 1).

Safety and Tolerability

Basimglurant MR at daily doses of 0.5 and 1.5 mg for 6 weeks was generally safe and well tolerated. The overall proportion of patients withdrawn because of AEs was similar across study arms (4.6%, 5.4%, and 7.2% in the placebo arm, 0.5-mg basimglurant MR arm, and 1.5-mg basimglurant MR arm, respectively). The AEs occurring at an incidence of 5% or higher in any treatment arm are given in **Table 3**.

The most frequent AEs, occurring in the nervous system disorders class, were dizziness (37 [11.1%] of patients), somnolence (30 [9.0%]), and headache (28 [8.4%]). The incidence of dizziness was dose related (26 [23.4%] patients in the 1.5-mg basimglurant MR arm compared with 5 [4.5%] in the 0.5-mg basimglurant MR arm and 6 [5.5%] in the placebo arm). Mild dizziness AEs were reported by 26 patients (70.3%), moderate by 10 (27.0%), and severe by 1 (2.7%). With the exception of 2 patients (1 in each active arm), all dizziness AEs resolved without sequelae. Dizziness AEs were generally transient and resolved without intervention after several days, and most reported no accompanying events, such as vertigo, nausea, vomiting, ataxia, headache, or syncope. One patient in the 1.5-mg basimglurant MR arm reported severe dizziness and vertigo concurrently and was withdrawn.

For AEs of suicidality and hepatic disorders, no clear association to basimglurant MR treatment was noted. The suicidal ideation AE occurred in 1 patient (0.9%) in the 0.5-mg basimglurant MR arm, 1 patient (0.9%) in the 1.5-mg basimglurant MR arm, and no patients in the placebo arm. Hepatic disorders (nonserious elevations of aspartate aminotransferase, alanine aminotransferase, and bilirubin) occurred with higher frequency in the placebo arm compared with the basimglurant MR arms. Mania was reported by 2 patients in the 1.5-mg basimglurant MR arm, leading to withdrawal of both patients from the study. In each case, the AE resolved spontaneously. No clinically relevant changes in laboratory parameters, vital signs, electrocardiographic parameters, or weight indicative of any treatment-emergent AE were observed during the study. There were 6 serious AEs: 2 in the placebo arm, 3 in the 0.5-mg basimglurant MR arm, and 1 in the 1.5-mg basimglurant MR arm. One serious AE in the 0.5-mg basimglurant MR arm was considered by the investigator to be related (remotely) to treatment (acute renal failure). The serious AE resolved without sequelae.

Discussion

This was the first large-scale, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of basimglurant MR as adjunctive treatment in a sample of patients with MDD having inadequate response to 1 to 3 adequate courses of antidepressant treatment during the current episode. No difference was observed on the study's powered primary outcome measure, the clinician-rated MADRS score change from baseline to end of treatment, between adjunctive basimglurant MR vs placebo. Nonetheless, adjunctive treatment with 1.5-mg basimglurant MR revealed an antidepressant effect across secondary and exploratory end points. Greater improvements were seen in patient-rated end points, such as the patient-

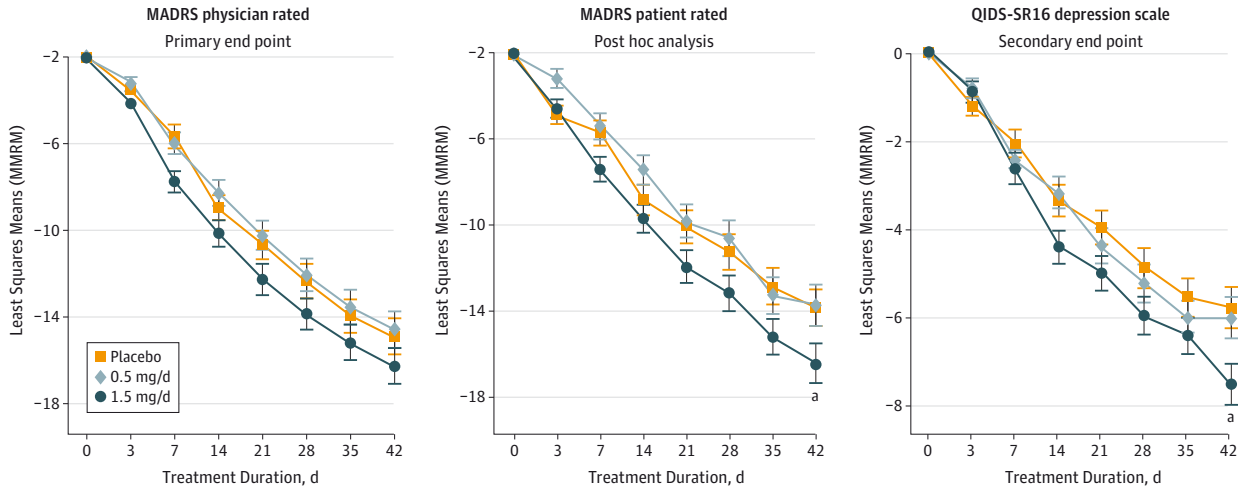
Table 1. Demographics and Clinical Characteristics at Baseline[a]

Characteristic	Basimglurant MR 0.5 mg (n = 112)	Basimglurant MR 1.5 mg (n = 111)	Placebo (n = 109)
Sex			
Male	42 (37.5)	34 (30.6)	40 (36.7)
Female	70 (62.5)	77 (69.4)	69 (63.3)
Age, y			
Mean (SD)	45.8 (10.8)	47 (17.1)	47.1 (11.3)
25th, 50th, and 75th percentiles	39, 46, 54	39, 47, 56	40, 49, 55
Range	21-70	23-69	21-68
Race			
White	77 (68.8)	82 (73.9)	81 (74.3)
Black	15 (13.4)	15 (13.5)	10 (9.2)
Asian	14 (12.5)	13 (11.7)	14 (12.8)
Other	6 (5.4)	1 (0.9)	4 (3.7)
Primary diagnosis			
MDD			
Single episode	10 (8.9)	11 (9.9)	12 (11.0)
Recurrent	102 (91.1)	100 (90.1)	97 (89.0)
Lifetime episodes			
Mean (SD)	4.2 (3.2)	4.0 (3.0)	5.0 (8.9)
25th, 50th, and 75th percentiles	2, 3, 5	2, 3, 5	2, 3, 6
Length of current episode, y			
Mean (median)	0.82 (0.47)	0.93 (0.43)	0.93 (0.43)
25th, 50th, and 75th percentiles	0.30, 0.47, 0.72	0.27, 0.43, 0.91	0.25, 0.42, 0.76
No. of treatment failures			
1	90 (80.4)	91 (82.0)	91 (83.5)
2	19 (17.0)	14 (12.6)	13 (11.9)
3	3 (2.8)	5 (4.5)	5 (4.6)
Baseline disease assessments			
MADRS			
Mean (SD)	31.1 (3.9)	31.3 (4.6)	31.1 (4.7)
25th, 50th, and 75th percentiles	29, 31, 34	28, 31, 34	28, 30, 34
QIDS-SR16			
Mean (SD)	14.3 (3.5)	14.3 (3.3)	14.1 (3.7)
25th, 50th, and 75th percentiles	12, 14, 16	12, 14, 16	12, 14, 16
CGI-S			
Mean (SD)	4.6 (0.5)	4.6 (0.5)	4.6 (0.5)
25th, 50th, and 75th percentiles	4, 5, 5	4, 5, 5	4, 5, 5
SDS (items 2-3)			
Mean (SD)	13.8 (4.0)	13.5 (3.6)	13.2 (3.7)
25th, 50th, and 75th percentiles	20, 26, 32	21, 26, 31	18, 25, 30
Q-LES-Q-SF			
Mean (SD)	32.1 (6.5)	32.3 (7.3)	32.8 (6.3)
25th, 50th, and 75th percentiles	28, 32, 37	2, 33, 37	29, 33, 37
Adjunctive therapy			
SSRIs			
Sertraline hydrochloride	35 (31.2)	24 (21.6)	36 (33.0)
Citalopram hydrobromide	18 (16.1)	18 (16.2)	13 (11.9)
Escitalopram oxalate	17 (15.2)	17 (15.3)	18 (16.5)
Paroxetine hydrochloride and mesylate	11 (9.8)	11 (9.9)	14 (12.8)
Fluoxetine hydrochloride	10 (8.9)	13 (11.7)	9 (8.3)
SNRIs			
Venlafaxine hydrochloride	8 (7.1)	15 (13.5)	10 (9.2)
Duloxetine hydrochloride	9 (8.0)	9 (8.1)	6 (5.5)
Desvenlafaxine	2 (1.8)	2 (1.8)	0
Milnacipran hydrochloride	1 (0.9)	2 (1.8)	2 (1.8)

Abbreviations: CGI-S, Clinical Global Impression–Severity; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MR, modified release; QIDS-SR16, 16-item Quick Inventory of Depressive Symptomatology–Self Report; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire Short Form; SDS, Sheehan Disability Scale; SNRI, serotonin or norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

Figure 2. Total Score Mean (SEM) Change From Baseline for the Clinician-Rated Montgomery-Åsberg Depression Rating Scale (MADRS), Patient-Rated MADRS, and 16-Item Quick Inventory of Depressive Symptomatology–Self-Report (QIDS-SR16) (Intent-to-Treat Sample)



MMRM indicates mixed-effects model for repeated measures. Error bars indicate SEMs.

[a] $P < .05$ (2-sided, unadjusted for multiple comparisons) for 1.5 mg vs placebo. Only showing day 42 testing.

Table 2. Overview of Primary, Secondary, and Exploratory End Points at Day 42 (Intent-to-Treat Sample)

	Basimglurant MR				
	0.5 mg (n = 112)		1.5 mg (n = 111)		Placebo LS Mean (n = 109)
End Point	LS Mean (SE)	*P* Value	LS Mean (SE)	*P* Value	
Primary efficacy end point					
MADRS (overall *P* = .07)[a,b]	−14.1 (0.9)	.74[c]	−16.1 (0.9)	.42[c]	−14.6 (0.9)
Secondary efficacy end points					
QIDS-SR16 (overall *P* = .11)[b]	−6.0 (0.5)	.72[d]	−7.5 (0.5)	.009[d]	−5.8 (0.5)
CGI-S (overall *P* = .40)[e]	−1.25 (0.11)	.45[d]	−1.49 (0.12)	.54[d]	−1.39 (0.11)
CGI-I (overall *P* = .14)[e]	2.58 (0.11)	.30[d]	2.21 (0.10)	.14[d]	2.41 (0.10)
PGI-I (overall *P* = .14)[e]	2.70 (0.11)	.933[d]	2.41 (0.12)	.09[d]	2.63 (0.10)
MADRS responders (overall *P* = .46)[a,f]	41.96	.50[g]	50.45	.59[g]	46.79
MADRS remissions (overall *P* = .32)[a,h]	26.79	.66[g]	36.04	.39[g]	30.28
Exploratory efficacy end points					
SDS (items 2-3) (overall *P* = .14)	−5.1 (0.6)	.94[d]	−6.4 (0.6)	.09[d]	−5.1 (0.6)
Q-LES-Q-SF (overall *P* = .07)	11.5 (0.9)	.37[d]	13.2 (0.9)	.02[d]	10.4 (0.9)
Post hoc analysis					
Patient-rated MADRS (overall *P* = .03)[b]	−13.1 (1.0)	.91[d]	−16.2 (1.0)	.04[d]	−13.3 (1.0)

Abbreviations: CGI-I, Clinical Global Impression–Improvement; CGI-S, Clinical Global Impression–Severity; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed-effects model for repeated measures; MR, modified release; PGI-I, Patient Global Impression–Improvement; QIDS-SR16, 16-item Quick Inventory of Depressive Symptomatology–Self Report; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire Short Form; SDS, Sheehan Disability Scale.

[a] Clinician-rated MADRS.

[b] Results from MMRM analysis, including LS means of the change from baseline.

[c] Adjusted 2-sided *P* values for treatment vs placebo.

[d] Unadjusted 2-sided *P* values for treatment vs placebo.

[e] Means and 2-sided *P* values from Wilcoxon test for treatment vs placebo.

[f] MADRS responder is defined as an MADRS total score of 50% at day 42 or less of baseline at day 42.

[g] Unadjusted, 2-sided upper *P* values from Fisher exact test for treatment vs placebo.

[h] MADRS remission is defined as MADRS total score of 10 or less at day 42.

rated MADRS and the QIDS-SR16, at several time points, including the day 42 end point, whereas the clinician-rated MADRS primarily revealed improvements at earlier time points only. Of note, however, the correlation coefficient between the patient-level, clinician-reported MADRS and post hoc patient-reported MADRS scores at day 42 was 0.85, suggesting a reasonably strong association. A 0.5-mg dose of basimglurant MR was not effective compared with placebo.

Table 3. Adverse Events With Incidence of at Least 5% (in Any Arm)

Adverse Event	No. (%) of Patients		
	Basimglurant MR		
	0.5 mg (n = 112)	1.5 mg (n = 111)	Placebo (n = 109)
Dizziness	5 (4.5)	26 (23.4)	6 (5.5)
Somnolence	13 (11.6)	7 (6.3)	10 (9.2)
Headache	12 (10.7)	8 (7.2)	8 (7.3)
Insomnia	6 (5.4)	6 (5.4)	2 (1.8)
Nausea	6 (5.4)	8 (7.2)	13 (11.9)
Dry mouth	4 (3.6)	6 (5.4)	4 (3.7)
Nasopharyngitis	1 (0.9)	0	8 (7.3)

Abbreviation: MR, modified release.

The presence of a high placebo response during the trial may have undermined the ability of this trial to detect a significant statistical difference between the placebo and active treatment arms for the primary end point of clinician-rated MADRS. In a meta-analysis[35] of the magnitude of the placebo response rates across different studies of adjunctive therapy in depressive patients, separation of the active drug vs placebo became obscured when placebo response rates were higher than 40%, leading the authors to conclude that excessive placebo response is the most challenging obstacle for the development of new treatments in this patient population. In the current study, the response rate on the clinician-rated MADRS in the placebo group was 47%, which likely reduced the possibility of detecting an antidepressant effect of the active compound. Nevertheless, in this trial, the response rates for 1.5-mg basimglurant MR were still superior to placebo.

Overall, basimglurant MR was safe and well tolerated in combination with a selective serotonin reuptake inhibitor or serotonin or norepinephrine reuptake inhibitor, with mild transient dizziness as the most common emergent AE. Despite a higher incidence of AEs overall and AEs leading to withdrawal in patients receiving 1.5-mg basimglurant MR, completion rates were high and comparable in all groups. The incidence of mania in this study (approximately 2%) is consistent with previous studies[36,37] of antidepressant use in patients with MDD, including selective serotonin reuptake inhibitors, which can be interpreted as an indication of the antidepressant effect of basimglurant MR.

In an independent study[38] conducted in healthy volunteers (clinicaltrials.gov, NCT01483469) using a radiotracer technique with positron emission tomography, it was established that basimglurant is able to competitively bind to mGlu5 receptors. A correlation was established between plasma concentration and receptor occupancy. Assuming a similar pharmacokinetic-receptor occupancy association in patients vs healthy volunteers, plasma sampling in the current study population of patients with MDD confirmed that the mean steady-state concentrations would be expected to result in receptor occupancy of approximately 25% at 0.5 mg and 53% at 1.5 mg (Mallalieu et al, unpublished data, 2016).

Considering the primary end point was not met, it is possible that the study design was not able to detect a treatment effect for the compound, the study execution and/or conduct were flawed, or the scientific rationale that the compound is an effective antidepressant in humans is wrong. Because many of the sites recruited a relatively small number of patients (the study involved 59 investigational sites to recruit the 333 randomized patients), it is not possible to comprehensively evaluate the effect of investigational site or its interaction with other model terms on the statistical analysis of the efficacy results. Despite these concerns, signs of efficacy were noted in some secondary outcomes for 1.5-mg basimglurant MR, which were clearer for patient-rated measures of depressive symptoms. There is an apparent discrepancy in how patients in the study reported improvements in their depressive symptoms compared with clinicians, as evidenced by data from the QIDS-SR16 and patient-rated MADRS vs the clinician-rated MADRS. In this context, MADRS was originally designed to detect the treatment effect of monoaminergic antidepressants,[26] resulting in the exclusion of items that may be relevant to treatment effects emerging from therapeutics with a different mechanism of action. In contrast, the clinician-rated and patient-rated QIDS-SR16 measures were developed to assess all the symptom domains relevant to the diagnosis of an MDD episode. In fact, in this study, improvements were observed on the QIDS-SR16 items of hypersomnia and general interest (P = .03 and .04, respectively) and feeling slowed down and energy levels (P = .08 and .09, respectively), suggesting that this scale covers relevant symptoms of depression not adequately addressed in the MADRS.

Conclusions

We could not find any effect of adjunctive basimglurant MR on the a priori primary outcome of clinician-reported MADRS. However, adjunctive basimglurant 1.5 mg MR daily showed an antidepressant effect across secondary end points, particularly in patient-rated measures. We believe these findings, combined with good tolerability, warrant further investigation with this compound in depressive disorders.

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