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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

Author(s): Daniel Umbricht, MD[a,*]; Markus Niggli, PhD[b]; Patricia Sanwald-Ducray, PhD[a]; Dennis Deptula, PhD[c]; Rema Moore, MS[c]; Waltraud Grünbauer, PhD[a]; Lauren Boak, PhD[d]; and Paulo Fontoura, MD, PhD[d]

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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

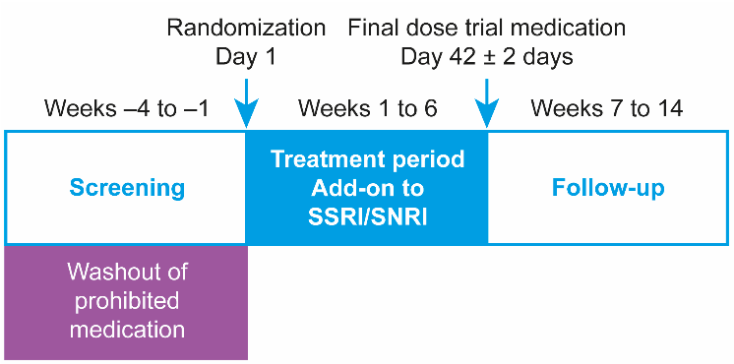
	Placebo		**Decoglurant 5 mg**		**Decoglurant 15 mg**		**Decoglurant 30 mg**	
	***n* = 86**		***n* = 89**		***n* = 88**		***n* = 47**	
	Centralized	**Site**	**Centralized**	**Site**	**Centralized**	**Site**	**Centralized**	**Site**
Change in MADRS total score[a]								
Mean (SD)	−11.8 (11.2)	−14.5 (10.1)	−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

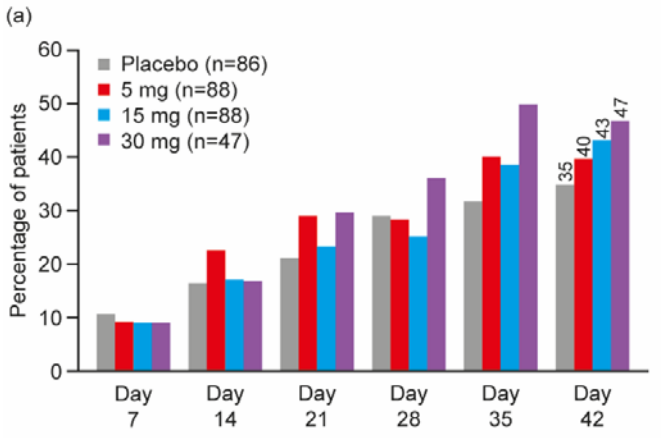


Schedule of endpoint assessments

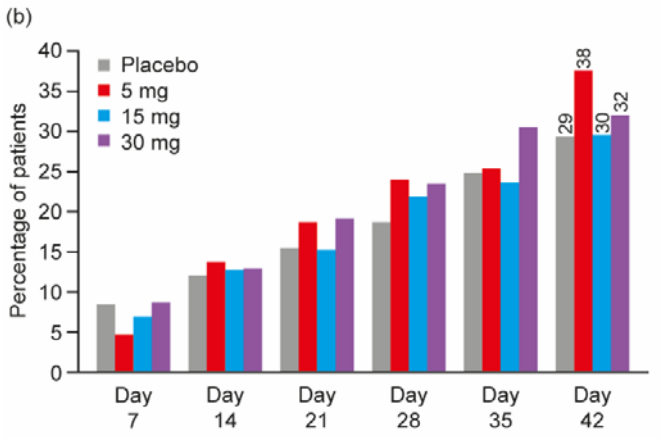
Scale	Screening	Baseline		W1	W2	W3	W4	W5	W6		W8	W10	W14
MADRS	CR	Site	CR	CR	CR	CR	CR	CR	Site	CR	CR	CR	CR
CGI-S	CR	Site	CR	CR	CR	CR	CR	CR	Site	CR	CR	CR	CR
CANTAB	Pt	Pt		Pt					Pt				
CGI-I									Site				
IDS-SR30	Pt	Pt		Pt	Pt	Pt	Pt	Pt	Pt		Pt	Pt	Pt
PGI				Pt	Pt	Pt	Pt	Pt	Pt				Pt
CPFQ		Pt							Pt			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