Randomized Placebo-Controlled Phase 2 Study of Extended-Release Ketamine Tablets (R-107) for Treatment-Resistant Depression – the BEDROC Study

Paul Glue (paul.glue@otago.ac.nz)
University of Otago https://orcid.org/0000-0002-7305-2800

Paul Glue
University of Otago

Colleen Loo
Black Dog Institute, University of New South Wales

Johnson Fam
Singapore General Hospital

Hsien-Yuan Lane
China Medical University Hospital.

Allan Young
Kings College London

Peter Surnam
Douglas Pharmaceuticals Ltd

Article

Keywords:

Posted Date: October 31st, 2023

DOI: https://doi.org/10.21203/rs.3.rs-3501826/v1

Additional Declarations: Yes there is potential Competing Interest. PG has a research contract with Douglas Pharmaceuticals to develop novel ketamine formulations, and is named on a patent for R-107. CL is on the Clinical Advisory Board for Douglas Pharmaceuticals and has received fees for attending Janssen Cilag advisory board meetings AHY is a consultant to Johnson & Johnson and Livanova. He has given paid lectures and sat on advisory boards for the following companies with drugs used in affective and related disorders: Astrazenaca, Eli Lilly, Lundbeck, Sunovion, Servier, Livanova, Janssen, Allegan, Bionomics, Sumitomo Dainippon Pharma, COMPASS. He has received honoraria for attending advisory boards and presenting talks at meetings organised by LivaNova. He is the Principal Investigator of trials of Esketamine, Vagus Nerve Stimulation, and Psilocybin in Depression. He has received grant funding(past and present) from NIMH(USA);

CIHR(Canada); NARSAD(USA); Stanley Medical Research Institute(USA); MRC(UK); Wellcome Trust(UK); Royal College of Physicians(Edin); BMA(UK); UBC-VGH Foundation(Canada); WEDC (Canada); CCS Depression Research Fund(Canada); MSFHR(Canada); NIHR(UK); Janssen(UK). PS is employed by DOuglas Pharmaceuticals. JF and H-YL have no disclosures,

Abstract

Ketamine has rapid-onset antidepressant activity in patients with treatment-resistant major depression (TRD). The safety and tolerability of racemic ketamine may be improved if given orally, as an extended release tablet (R-107), compared with other routes of administration. In this phase 2 multicentre clinical trial, adult patients with TRD and Montgomery-Asberg Depression Rating Scale (MADRS) scores ≥20 received open label R-107 tablets 120mg/day for 5 days and were assessed on Day 8 (enrichment phase). On Day 8, responders (MADRS scores ≤12 and reduction ≥50%) were randomized on a 1:1:1:1:1 basis to receive double-blind R-107 doses of 30, 60, 120, or 180mg, or placebo, twice weekly for a further 12 weeks. Non-responders on Day 8 exited the study. The primary endpoint was least square mean change in MADRS for each active treatment compared with placebo at 13 weeks, starting with the 180mg dose, using a fixed sequence step-down closed test procedure. Between August 2016 and April 2020, 329 individuals were screened for eligibility, 231 entered the open label enrichment phase (Days 1-8), and 168 responders were randomized to double-blind treatment. The primary objective was met; the least square mean difference of MADRS score for the 180mg tablet group and placebo was -6.1 (95% CI 1.0-11.16, p=0·019) at 13 weeks. Relapse rates during double-blind treatment showed a dose-response, from 70.6% for placebo, to 42.9% for 180mg. Tolerability was excellent, with no changes in blood pressure, minimal reports of sedation, and minimal dissociation. The most common adverse events were headache, dizziness and anxiety. During the randomised phase of the study most patient dosing occurred at home. R-107 tablets were effective, safe and well-tolerated in a patient population with TRD, enriched for initial response to R-107 tablets. Clinical Trial Registration ACTRN12618001042235.

Introduction

Over the past 2 decades, there has been a growing evidence base demonstrating the rapid-onset antidepressant properties of ketamine in patients with treatment resistant depression (TRD). The majority of published research has been with off-label use of racemic ketamine,[1] with a more recent regulatory approval of esketamine for TRD.[2] Ketamine and esketamine can be effectively administered via multiple routes, although dose ranges and bioavailability vary by route of administration.[3]

The pharmacology of ketamine relating to its antidepressant activity has been linked to several of its metabolites, including norketamine and the hydronorketamines.[4,5] After oral dosing, pharmacokinetic exposure to norketamine and the hydronorketamines is considerably more prolonged than exposure to ketamine.[6] Furthermore, ketamine is still active as an antidepressant even when dosed by routes where bioavailability of parent ketamine is low.[7] A synthesis of these observations suggests that ketamine may be acting as a prodrug, where its antidepressant activity is substantially due to its metabolites. A meta-analysis of ketamine formulations identified that formulations that maximize first pass metabolism of ketamine and delay time to maximum concentrations were better tolerated (less dissociation) and safer (less blood pressure change) than formulations which lack those characteristics.[8] We hypothesized that an extended release tablet formulation of ketamine could be an effective and well tolerated treatment option for patients with TRD. Details of the formulation and its pharmacokinetic profile have been published.[9,10] We report here on a multicentre Phase 2 study of the extended release ketamine tablets (R-107) in patients with TRD.

The study design is shown in Figure 1. We chose this design due to observations that acute antidepressant clinical trials in non-TRD depression have high failure rates (inability to separate clinical response between active and placebo arms), as high as 50%.[11,12] Failure rates can be reduced by using an enrichment design, in which non-responders to acute treatment are excluded, followed by a subsequent relapse-prevention phase in treatment responders;[13] study failure rates using this design are as low as 25%. A similar design was used in Daly's pivotal esketamine randomized withdrawal study.[14] We included a dose-finding component in our double-blind relapse prevention phase as it was unclear what the effective oral dose range might be.

Results

Between August 2016 and April 2020, 329 individuals were screened for eligibility, 231 entered the open-label enrichment phase (Days 1–5). At day 8 assessment, 132/231 (57.1%) of participants were in remission, and 168/231 (72.7%) were responders. After exclusion of nonresponders, the 168 responders were randomized to double-blind treatment (see Consort diagram (Fig. 2)). Participant demographic details are provided in Table 1. Mean pretreatment MADRS scores were approximately 30, and mean number of failed antidepressant trials was approximately 4.8 (Table 1). By the end of the study (week 13), 100 participants had discontinued of which 94 were for lack of efficacy as defined by a MADRS total score of ≥ 22 (placebo = 26, 30mg = 22, 60mg = 19, 120mg = 16, and 180mg = 11) (see Fig. 2). The proportion of participants who completed the study ranged from 29.7% in the placebo arm through to 56.2% for the 180mg dose arm, with higher proportions associated with higher R-107 doses. Treatment compliance was high with almost all participants (96.4%) reported to have compliance of 80% or more (at home and in clinic).

Table 1
Baseline characteristics of study participants enrolled in the randomized double-blind phase. ADs: antidepressants.

Dose arm	Placebo	R-107 30mg	R-107 60mg	R-107 120mg	R-107 180mg
n	37	34	34	31	32
Mean (SD) age	43.7 (15.4)	44.6 (12.9)	42.5 (15.8)	47.2 (13.8)	46.8 (11.9)
Gender (M/F)	22/15	18/16	17/16	13/18	21/11
Number of prior depressive episodes	3.66 (7.45)	2.17 (2.06)	2.80 (3.09)	3.33 (2.71)	1.75 (1.59)
Treatment resistance (mean number of past failed ADs in this episode)	4.69	4.93	4.62	4.85	4.59
Failed ECT pre-study	2	4	1	5	2
Number taking ADs pre-study entry	32 (86.5%)	25 (73.5%)	25 (73.5%)	22 (71.0%)	24 (75.0%)
Day 1 MADRS score (SD)	30.2 (4.5)	29.9 (4.1)	29.3 (5.8)	31.4 (5.2)	29.9 (4.6)

Primary Outcome

Numerically, greater mean reductions in the MADRS total score from baseline to Day 92 were observed in all treatment groups compared with placebo (R-107 30 mg: 1.9 [95% CI: −3.08 to 6.92], p = 0.450; 60 mg: 0.7 [95% CI: −4.32 to 5.70], p = 0.785; 120 mg: 4.5 [95% CI: −0.60 to 9.69], p = 0.083). The largest reduction was in the 180 mg treatment group: 6.1 [95% CI: 1.00 to 11.16; p = 0.019] and this result was statistically significant.

Secondary Efficacy Outcomes

During the open-label enrichment phase (Days 1–8), there was mean reduction in MADRS total score of 18.5 points (95% CI: 17.37 to 19.69) at Day 8. A total of 132 participants (57.1%) of the 231 enrolled in the enrichment phase achieved remission with a MADRS total score ≤ 10 at Day 8. A total of 168 participants (72.7%) of the 231 patients enrolled in the enrichment phase achieved a response to treatment, defined as ≥ 50% reduction from baseline in MADRS score at Day 8.

Rates of remission and response at week 13 were numerically greater for the active treatment arms compared with placebo, however these were not statistically significant (remission), or were significant for only the 120mg dose group for treatment response (48% vs 24.3%, p = 0.046). Compared with baseline, CGI-S scores improved in participants randomized to ketamine, however this was not statistically significant compared with placebo. With the exception of the 60mg dose group, the 120mg and 180mg ketamine dose groups had higher probability of improvement in depression severity from the subject's perspective, using the PGI-I scale, compared with the placebo group (OR (95% CI) 30mg: 0.52 (0.09, 2.78); 60mg: 1.62 (0.36, 7.42); 120mg: 0.28 (0.06, 1.25); 180mg: 0.82 (0.19, 3.51) ORs < 1 signify higher probabilities for the active treatment group for lower categories compared with the placebo group) .

Temporal trends in relapse by dose group are shown in Fig. 3. The majority of relapses occurred within the first 4 weeks. The median relapse time after randomization increased with higher R-107 doses (placebo: 45 days; 30mg: 28 days; 60 mg: 56 days; 120 mg: 64 days; and 180mg: >85 days). The difference in the restricted mean survival time for the 180 mg treatment group was significantly greater compared with the placebo group (19.0 [95% CI: 4.9 to 33.1]).

Safety Outcomes

Adverse events were rated predose and post dose prior to leaving clinic, and on scheduled telephone calls. During the open-label enrichment phase, the most common adverse events included dizziness, headache, dissociation, feeling abnormal, fatigue, and nausea. 26 participants (11.6%) reported dissociation. Mean CADSS scores were < 3 for all participants throughout this phase. Mean blood pressure changes after 5 days of open-label 120mg daily dosing in the enrichment phase were systolic and diastolic blood pressure changes of -1.2mmHg and − 0.1mmHg, respectively.

The most common side effects reported in the double-blind treatment phase are shown in Table 2. The majority of these were of mild intensity (131 subjects; 56.7%) or moderate intensity (42 subjects; 18.2%). Symptoms of cystitis, as assessed by the BPIC-SS, remained low (< 3 points) throughout the study, and were not different

between the placebo and 180mg dose groups. Mean CADSS scores were < 1 point at all visits during the double-blind phase of the study. Sedation of mild severity was reported by a total of 5 participants (30mg – n = 4; 120mg – n = 1). Mean CADSS scores were < 1 point at all timepoints during this phase of the study. Mean ratings of cystitis symptoms using the BPIC questionnaire remained less than 3 points throughout the study, out of a maximum of 38, with no differences between placebo and 180mg dose groups.

Table 2
Treatment-emergent adverse events occurring in ≥ 10% of study participants enrolled in the randomized double-blind phase. *URTI: upper respiratory tract infection.

Dose arm	Placebo (n = 37)	R-107 30mg (n = 34)	R-107 60mg (n = 34)	R-107 120mg (n = 31)	R-107 180mg (n = 32)
Headache	6 (16%)	10 (29%)	11 (32%)	6 (19%)	6 (19%)
Dizziness	3 (8%)	4 (12%)	5 (15%)	5 (16%)	9 (28%)
Anxiety	2 (5%)	3 (9%)	1 (3%)	6 (19%)	6 (19%)
Depression	2 (5%)	4 (12%)	5 (15%)	2 (6%)	3 (9%)
Dissociation	0 (0%)	1 (3%)	1 (3%)	2 (6%)	5 (5%)
Nausea	3 (8%)	3 (9%)	2 (6%)	3 (10%)	5 (16%)
Feeling abnormal	2 (5%)	5 (15%)	1 (3%)	2 (6%)	3 (9%)
Fatigue	3 (8%)	1 (3%)	0 (0%)	4 (13%)	2 (6%)
URTI*	4 (11%)	3 (9%)	2 (6%)	2 (6%)	3 (9%)

During double-blind treatment, there were 10 severe adverse events in 8 participants: severe headache (30mg and 60mg dose groups); severe depression (120mg and 180mg dose groups); completed suicide at day 42 in a 65-year-old male (180mg dose group); non-cardiac chest pain (60mg dose group); nausea (30mg dose group); intervertebral disc protrusion (120mg dose group); and nephrolithiasis and ureterolithiasis (in 1 participant in the placebo group). Five subjects experienced serious adverse events (SAEs): three participants in the 180 mg group (wound dehiscence (n = 1), suicidal ideation (n = 1), and completed suicide (n = 1); one participant in the 60 mg group had non-cardiac chest pain; and one participant in the placebo group had a urinary calculus. None of the SAEs were considered treatment related (the suicide was considered by the site PI to be due to the disease under study), and all SAEs resolved except for the completed suicide.

There were no changes of note in safety laboratory tests, urinalyses, vital signs, body weights or ECGs. There were no changes of note in BPRS + or MOCA scores during the study.

Discussion

In this study, 231 patients with TRD were treated with R-107 120mg/day for 5 days, and 168 (72.7%) were included as an enriched responder population who were randomized to a range of double-blind R-107 doses or placebo for the next 12 weeks. In this double-blind phase, the 180mg dose given twice weekly showed statistically significant and clinically meaningful improvement in depressive symptoms based on MADRS score compared with placebo, with a group-treatment difference of 6.1. Side effects commonly observed in

clinical trials of injected or intranasal ketamine (e.g. dissociation, sedation, increased blood pressure) were minimal, and overall tolerability was good. Most patient dosing during the double-blind phase occurred at home.

Acute placebo-controlled antidepressant clinical trials in non-TRD patients have high failure rates, up to 50%.[11,12] Study failure rates in patients with TRD may be similarly high (47%), based on the proportion of industry-funded studies of ketamine/esketamine registered on clinicaltrials.gov between 2010–2022, where no results have been published. As discussed in the introduction, failure rates (inability to separate responses between active and placebo arms) can be reduced by using an enrichment design to remove treatment nonresponders, prior to a double-blind relapse-prevention phase.[13] Failure rate across all studies using this design was 25%.[13] We included a dose-finding component in the double-blind phase of the present study as it was not clear what the effective oral dose range might be. The R-107 dose used in the enrichment phase (120mg daily for 5 days) was based on observations from case reports from patients with pain and TRD receiving continuous ketamine infusions for 5 days, who reported mood improvements occurring by 24–72 hours.[15] The tablet formulation's sustained exposure to ketamine and norketamine over 24 hours after once-daily dosing provided a similar prolonged pharmacokinetic exposure.[9] Ketamine dosing was open-label during the enrichment phase, therefore the high remission (57.1%) and response (72.7%) rates for participants during this phase have to be considered cautiously due to likely expectation effects.[16] During the double-blind treatment phase, clear-dose responses were observed, for proportion of patients relapsing and median time to relapse, and there were dose-related trends for reductions in the MADRS total score. Most relapses in the 0-120mg dose groups occurred within 1 month of randomization (Fig. 3). Only the mean between-group treatment difference between the 180mg and placebo groups (-6.1) was statistically significant, and this value exceeds the minimum clinically important difference threshold for antidepressants reported in the literature.[17]

The relapse rates between weeks 2 and 13 in patients randomized to the placebo and 180mg dose groups (70.3% and 43.7% respectively) are both higher than those reported in a meta-analysis of relapse-prevention studies of antidepressants in non-TRD patients[13] and in TRD patients enrolled in an esketamine randomized withdrawal study[14] (see Table 3). This could be due to the much shorter duration of open label dosing in the present study (5 days) compared with 16 weeks in patients with TRD[14], and a mean of 16.4 weeks in non-TRD depressed patients.[13] These longer dosing periods prior to randomized withdrawal could select for stable responders, which would reduce subsequent relapse rates.

Table 3
Comparison of relapse rates in relapse-prevention antidepressant trials in TRD and non-TRD patient populations. Randomized to antidepressant population for the present study is the 180mg twice weekly cohort. AD: antidepressant; PBO: placebo

Study	Population; duration of open-label dosing before randomization	Relapse/ total population	Randomized to Antidepressant	Randomized to Placebo	AD relapse ratio	PBO relapse ratio	AD/PBO relapse ratio
Glue 2010	Non-TRD 16.4 weeks	Relapse	1177	1758	22.5	43.6	0.51
		Total	5237	4031			
Daly 2019	TRD 16 weeks	Relapse	16	34	25.8	57.6	0.45
		Total	62	59			
Present study	TRD 5 days	Relapse	14	26	43.7	70.3	0.62
		Total	32	37			

Many of the secondary efficacy outcome variables also showed dose-related trends compared with placebo, however these were not statistically significant, presumably because of small dose group sizes, which may have reduced statistical power.

Commonly-reported adverse events during the open-label enrichment phase included dizziness, headache, dissociation, feeling abnormal, fatigue, and nausea. The intensity of dissociation in the 26 participants (11.6%) who reported this adverse event was minor, as demonstrated by mean CADSS scores of 3 or less for all participants. The most common side effects reported in the double-blind relapse-prevention phase were headache, dizziness, anxiety, depressed mood and dissociation (Table 2), most of which were mild-moderate in intensity. Other notable differences from adverse events commonly reported after administration of ketamine or esketamine[18] were the absence of cardiovascular side effects, especially relating to increased blood pressure, low rates of dissociation, and also very low rates of sedation. Mean ratings of cystitis symptoms using the BPIC-SS questionnaire remained less than 3 points throughout the study, out of a maximum of 38, with no differences between placebo and 180mg dose groups.

Another common concern about most currently available ketamine and esketamine formulations is the risk of diversion and abuse.[19] The extended release ketamine tablets used in this study are exceptionally hard and difficult to shatter, due to annealing of polyethylene oxide during their manufacturing process.[10] This property may make this formulation less likely to be diverted for abuse, due to difficulty in manipulation of the tablets. We were not aware of any participants reporting craving for the tablets, and only one participant was removed from the study for lack of compliance. Most of the dosing of double-blind tablets after Day 8 occurred at home rather than in clinic, and clinic visits were brief, which participants anecdotally reported to be convenient. These attributes potentially improve scalability of ketamine use in the community, due to reduced need for in-clinic monitoring, and would also reduce costs associated with clinic visits.

There are several important limitations to the trial. The study design (enrichment followed by relapse prevention) was intended to reduce risk of study failure.[13] Because this type of design eliminates non-

responders prior to randomization, this strategy is likely to overestimate population levels of treatment response to R-107, and future unenriched clinical trials are needed to address this issue. There are relatively few data for efficacy and tolerability after oral ketamine dosing compared with intravenous or intranasal dosing, and it is not possible to directly compare the present study's findings with studies using non-oral routes of administration. This study included both participants established on antidepressants (n = 165), as well as those who were not on antidepressants (n = 60). Secondary analyses did not show differences in the acute response to ketamine (the mean (95%CI) reduction in MADRS score for those taking an antidepressant was −19.2 vs -16.6 for those not taking an antidepressant (-2.6 (-5.19 to 0.02)). Further larger studies are required to determine if these two populations respond differently to oral ketamine. Also, the protocol did not require patients to start a new antidepressant at the time of starting study medication, as this [?] design would have complicated interpretation of this intervention.

In conclusion, extended-release R-107 tablets were effective, safe and well-tolerated in an enriched patient population with TRD. Use of an extended-release oral dosage ketamine formulation may be advantageous compared with intranasal or intravenous dosing, in terms of reduced intensity of dissociation, lower risk of abuse, reduced frequency and intensity of sedative and cardiovascular side-effects, and improved convenience for administration in the community.

Online Methods

Study design and oversight

This Phase 2 multicentre clinical trial recruited participants from 20 psychiatric clinics in New Zealand, Australia, Singapore and Taiwan. The trial design included an initial 1 week open-label enrichment phase to exclude non-responders, followed by a 12-week double-blind relapse prevention phase in participants who were treatment responders in the enrichment phase (Fig. 1). The trial was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and Good Clinical Practice quality standards, and is reported in accordance with the CONSORT 2010 statement. The protocol, consent forms and associated documents were approved by local or national ethics committees. A copy of the protocol and statistical analysis plan are included with supplementary data. This study was prospectively registered (ACTRN12618001042235).

Patients

Adult patients (18–80 years) with DSM-5 major depressive disorder which was treatment resistant (failure to respond to adequate courses of at least two antidepressants), and who provided written informed consent, were eligible to enter screening. Patients' depression scores, assessed using the Montgomery-Asberg Depression Rating Scale (MADRS)[20] were 20 or higher during screening. Any concurrent antidepressant medication had to be at stable dosage ≥ 4 weeks prior to study entry, and during the study. Key exclusion criteria included having severe medical disorders, contraindications to the use of ketamine, clinically significant findings on physical examination, safety laboratory tests or ECGs, serious risk for suicide, recent history of alcohol or drug abuse, or a history of bipolar disorder, schizophrenia, or severe personality disorder. Detailed inclusion/exclusion criteria can be found in the study protocol (Supplementary Information).

Trial Procedures, Randomization and Blinding

Patients who met eligibility criteria and completed screening received open label R-107 tablets 120mg/day for 5 days (Days 1–5; enrichment phase). On Day 8, dosing responders (MADRS scores ≤ 12 and reduction ≥ 50% from baseline) were randomized on a 1:1:1:1:1 basis to receive double-blind R-107 doses of 30, 60, 120, or 180mg, or placebo, twice weekly for 12 weeks; non-responders exited the study. Each dose administered during the double-blind phase comprised 3 tablets which could contain 0, 30 or 60mg R-107, to make up the allocated dose. Active and placebo tablets dispensed during the trial were identical in appearance. Randomization was by an automated integrated web response system. All patients, and all people involved in the conduct of the clinical trial were blinded to treatment allocation. During the double-blind relapse prevention phase, there were weekly clinic visits up to week 6, and clinic visits every 4 weeks up to 13 weeks. Medication compliance was monitored by participants completing a dosing diary that they brought to clinic visits for checking, plus return of investigational product containers. Participants also received scheduled phone checks from investigators at the study sites to enquire about compliance, during these calls patients were asked if they had experienced any AE's. Patients who relapsed during double blind treatment (MADRS ≥ 22) were withdrawn from the study and could enter an open-label extension study.

Dose justification

The open-label R-107 used in the Day 1–5 enrichment phase had previously shown onset of antidepressant activity by day 2 of dosing in a pilot study of R-107 in patients with TRD.[9] This method of dosing was intended to provide continuous exposure to ketamine and its metabolites and to recreate exposures that would occur in a continuous ketamine infusion paradigm previously reported to have rapid onset antidepressant effects.[15] Doses used in the double-blind phase were intended to cover the range of oral doses reported to be active in a review of oral ketamine for depression.[21]

Endpoints

The primary efficacy endpoint was the change in MADRS total score from baseline in the randomized double-blind treatment phase (Day 8) to Day 92 (Week 13). This was evaluated with analysis of covariance (ANCOVA), with dose as a factor and baseline MADRS as a covariate. Time to relapse was another efficacy measure. Other efficacy measures included the Patient Global Impression-Improvement (PGI-I) and Clinical Global Improvement-Severity (CGI-S) scales.[22] Safety assessments included safety laboratory tests (haematology and biochemistry), ECGs, Montreal Cognitive Assessment (MoCA)[23] and verbal fluency tests, Columbia Suicide Severity Rating Scale (CSSRS)[24], bladder pain/interstitial cystitis symptom score (BPIC-SS)[25] and the four-item positive symptom subscale of Brief Psychiatric Rating Scale (BPRS+).[26] Tolerability assessments included reported adverse events, and CADSS (dissociation)[27] scores.

Sample size and statistical analysis

The sample size calculation was based on the superiority of R-107 to placebo by a magnitude of 6 MADRS units, using a standard deviation of change in MADRS of 7.5 units, a two-sided Type 1 error of 0.05, and a power of 80%. A closed testing procedure was assumed whereby each dose group was compared with the placebo group in descending dose order, and 26 subjects per group were required. Allowing for a 13% drop-out

rate and an attrition rate of 25% during the enrichment open-label phase, approximately 200 subjects were required initially in order to have 150 subjects randomized to five treatment groups at the start of the double-blind randomized treatment phase.

The primary endpoint, change in MADRS total score from baseline (Day 1) to Day 92, was analysed using ANCOVA. The analysis was based on differences in MADRS total scores at Day 92 from Day 1 MADRS total score, with dose as factor and baseline MADRS total score as a covariate. Missing values for the Day 92 MADRS total scores were imputed from the last available MADRS total score using a last observation carried forward approach, under the assumption that this was a conservative imputation (it was assumed that more relapses would occur in the placebo group, and that relapsed subjects would have deteriorated further had they remained in the study, so this imputation method was conservative in terms of the estimation of a treatment effect). This ensured the main analysis of the primary endpoint was not left unanalysable due to high relapse rates in some groups.

Role of the funding source

The study was co-designed by the funder and PG. The funder was responsible for trial execution, data collection and statistical analysis. The authors had full access to the trial data, and were responsible for data interpretation and writing of the manuscript.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at *****.

References

1. Nikolin, S., Rodgers, A., Schwaab, A., Bahji, A., Zarate, C. Jr, Vazquez, G., Loo, C. Ketamine for the treatment of major depression: a systematic review and meta-analysis. *EClinicalMedicine.*, *62*, 102127 (2023).
2. Kim, J., Farchione, T., Potter, A., Chen, Q., & Temple, R. Esketamine for treatment-resistant depression—first FDA-approved antidepressant in a new class. *New Engl J Med*, *381*, 1-4 (2019).
3. McIntyre, R. S., et al. Synthesizing the evidence for ketamine and esketamine in treatment-resistant depression: an international expert opinion on the available evidence and implementation. *Am J Psychiatry*, *178*, 383-399 (2021).
4. Highland, J. N. et al. Hydroxynorketamines: pharmacology and potential therapeutic applications. *Pharmacol Rev., 73*, 763-791 (2021).
5. Paul, R. K., et al. (R, S)-Ketamine metabolites (R, S)-norketamine and (2S, 6S)-hydroxynorketamine increase the mammalian target of rapamycin function. *Anesthesiology*, *121*, 149-159 (2014).
6. Hasan, M., et al. Chiral pharmacokinetics and metabolite profile of prolonged-release ketamine tablets in healthy human subjects. *Anesthesiology*, *135*, 326-339 (2021).
7. Domany, Y., et al. Repeated oral ketamine for out-patient treatment of resistant depression: randomised, double-blind, placebo-controlled, proof-of-concept study. *Br J Psychiatry*, *214*, 20-26. (2019).

8. Glue, P., Russell, B., & Medlicott, N. J. Influence of formulation and route of administration on ketamine's safety and tolerability: systematic review. *Eur J Clin Pharmacol*, *77*, 671-676 (2021).
9. Glue, P., Medlicott, N. J., Surman, P., Lam, F., Hung, N., & Hung, C. T. Ascending-dose study of controlled-release ketamine tablets in healthy volunteers: pharmacokinetics, pharmacodynamics, safety, and tolerability. *J Clin Pharmacol*, *60*, 751-757 (2020).
10. Glue P.W., Medlicott N.J., Surman P.W. Extended release pharmaceutical formulation and methods of treatment. U.S. Patent No. 11,471,416. 18 Oct 2022.
11. Khan, A., Mar, K. F., & Brown, W. A. The conundrum of depression clinical trials: one size does not fit all. *Int Clin Psychopharm*, *33*, 239 (2018).
12. Khin, N. A., Chen, Y. F., Yang, Y., Yang, P., & Laughren, T. P. Exploratory analyses of efficacy data from major depressive disorder trials submitted to the US Food and Drug Administration in support of new drug applications. *J Clin Psychiatry*, *72*, 6970 (2011).
13. Glue, P., Donovan, M. R., Kolluri, S., & Emir, B. Meta-analysis of relapse prevention antidepressant trials in depressive disorders. *Austral NZ J Psychiatry*, *44*, 697-705 (2010).
14. Daly, E. J., et al. Efficacy of esketamine nasal spray plus oral antidepressant treatment for relapse prevention in patients with treatment-resistant depression: a randomized clinical trial. *JAMA Psychiatry*, *76*, 893-903 (2019).
15. Correll, G. E., & Futter, G. E. Two case studies of patients with major depressive disorder given low-dose (subanesthetic) ketamine infusions. *Pain Med*, *7*, 92-95 (2006).
16. Brown, W. A. Expectation, the placebo effect and the response to treatment. *Rhode Island Med J*, *98*, 19 (2015).
17. Melander, H., Salmonson, T., Abadie, E., & van Zwieten-Boot, B. A regulatory Apologia—a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. *Eur Neuropsychopharm.* 18, 623-627 (2008).
18. Short, B., Fong, J., Galvez, V., Shelker, W., & Loo, C. K. Side-effects associated with ketamine use in depression: a systematic review. *Lancet Psychiatry*, *5*, 65-78 (2018).
19. Sanacora, G., Heimer, H., Hartman, D., Mathew, S. J., Frye, M., Nemeroff, C., & Robinson Beale, R. Balancing the promise and risks of ketamine treatment for mood disorders. *Neuropsychopharmacology*, *42*, 1179-1181 (2017).
20. Montgomery, S. A., & Åsberg, M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*, *134*, 382-389 (1979).
21. Schoevers, R. A., Chaves, T. V., Balukova, S. M., & Kortekaas, R. Oral ketamine for the treatment of pain and treatment-resistant depression. *Br J Psychiatry*, *208*, 108-113 (2016).
22. Busner, J., & Targum, S. D. The clinical global impressions scale: applying a research tool in clinical practice. *Psychiatry (Edgmont)*, *4*, 28. (2007).
23. Blair, M., et al. Depressive symptoms negatively impact Montreal Cognitive Assessment performance: a memory clinic experience. *Can J Neurol Sci*, *43*, 513-517 (2016).
24. Posner, K., et al. Columbia-suicide severity rating scale (C-SSRS). *New York, NY: Columbia University Medical Center*, *10*, (2008).

25. Humphrey, L., et al. The bladder pain/interstitial cystitis symptom score: development, validation, and identification of a cut score. *Eur Urology*, *61*, 271-279. (2012).
26. Overall, J. E., & Beller, S. A. The Brief Psychiatric Rating Scale (BPRS) in geropsychiatric research: I. Factor structure on an inpatient unit. *Journal of Gerontology*, *39*, 187-193 (1984).
27. Bremner, J. D., et al. Measurement of dissociative states with the clinician-administered dissociative states scale (CADSS). *J Trauma Stress*, *11*, 125-136. (1998).

Figures

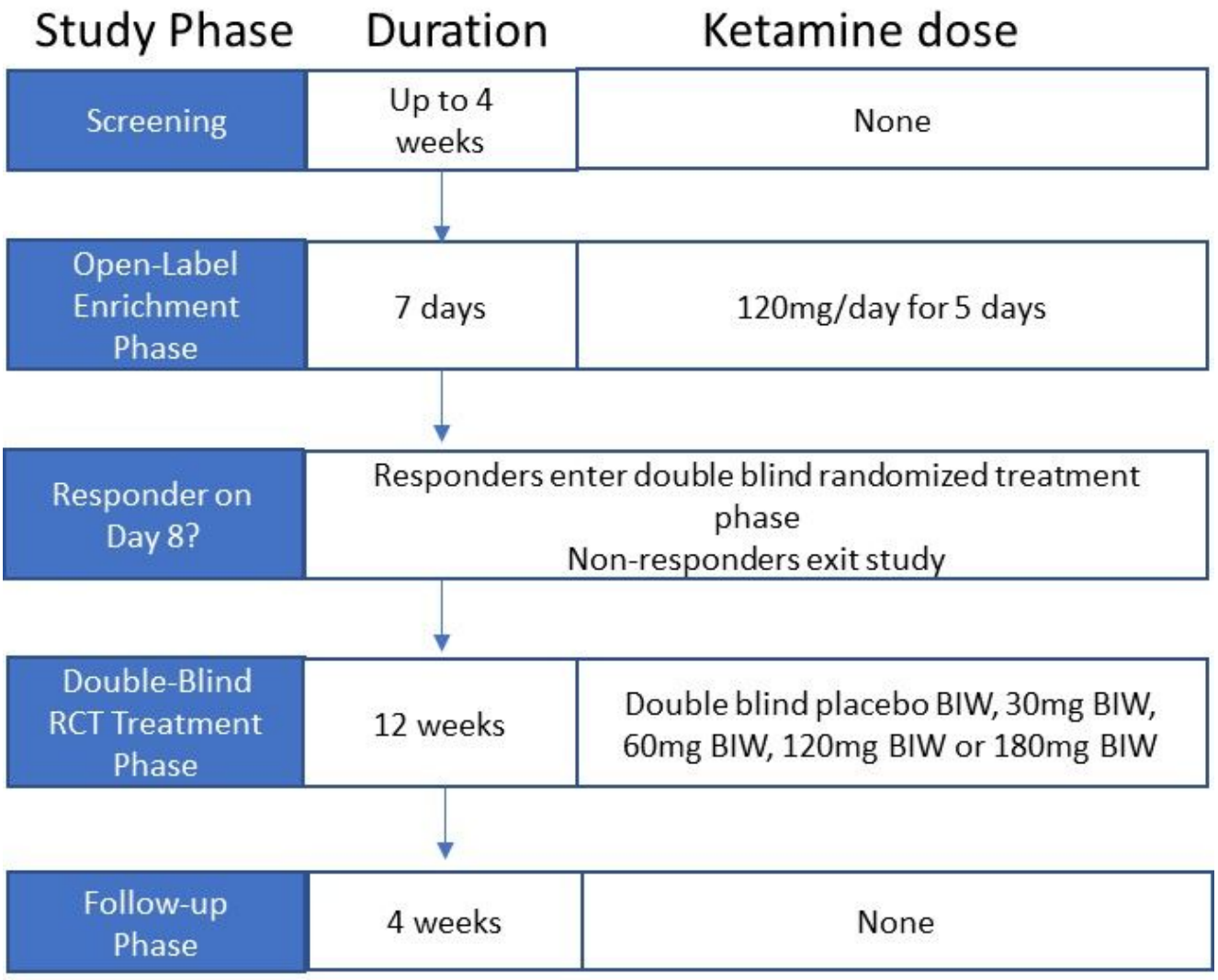

Figure 1

Study design: BIW: twice weekly dosing.

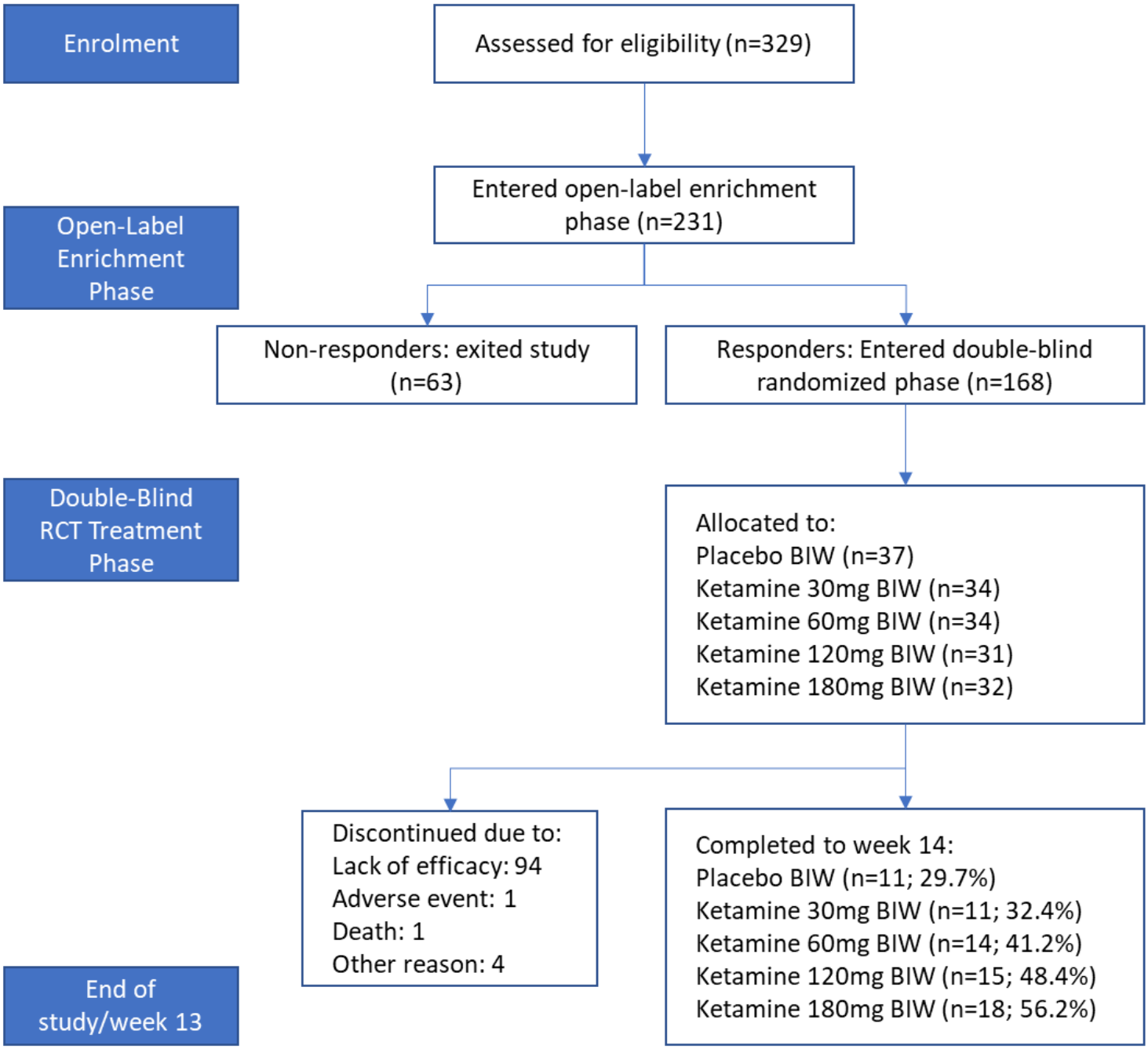

Figure 2

Disposition of Participants

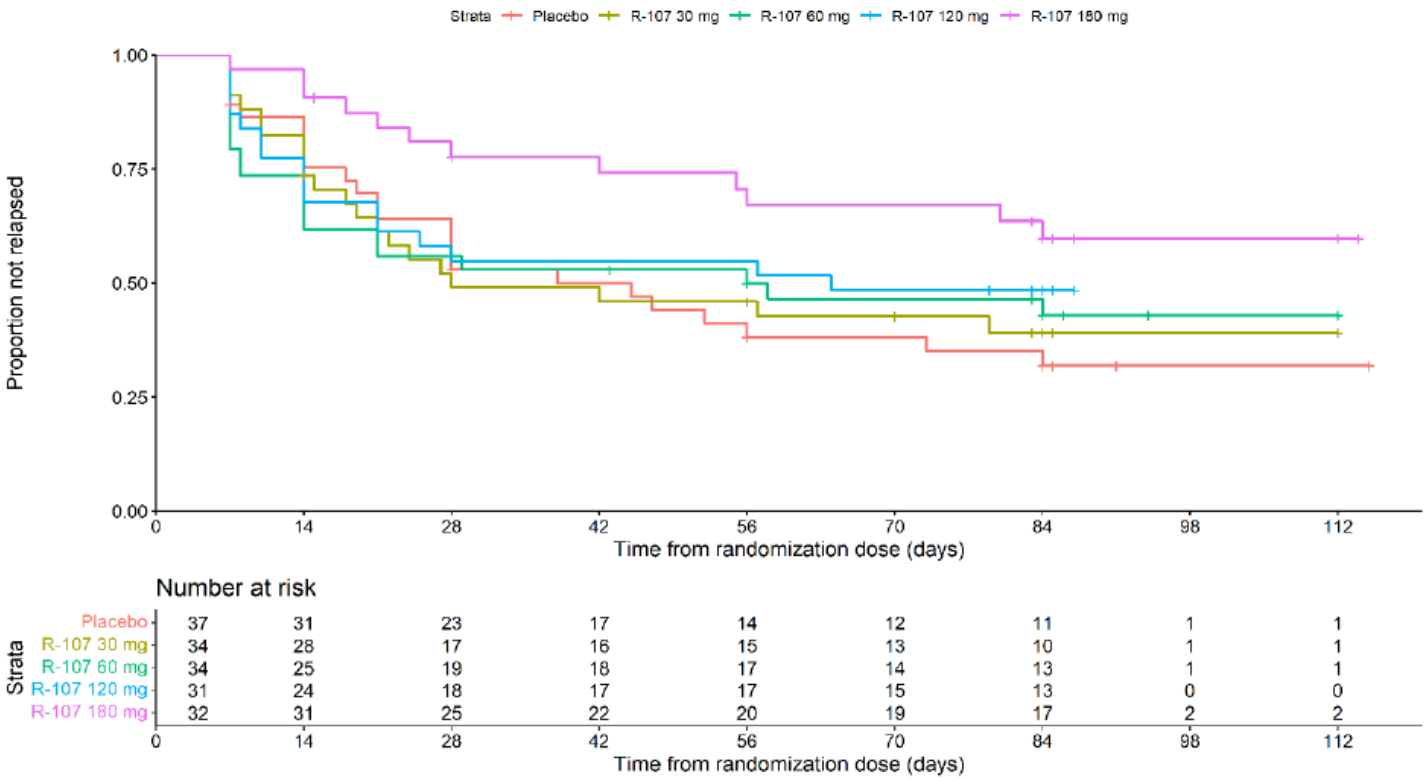

Figure 3

Kaplan-Meier estimates of time to relapse

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- BEDROCProtocolfinalV5.026FEB2019.pdf
- CONSORT2010ChecklistforNatMed.doc