Rapid Onset and Sustained Efficacy of Onfasprodil (MIJ821), a Novel NR2B Negative Allosteric Modulator, in Patients With Treatment-Resistant Depression:

A Phase 2, Randomized, Placebo-Controlled, Proof-of-Concept Study

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Abstract

Background: Onfasprodil (MIJ821) is a highly potent and novel selective NR2B subunit negative allosteric modulator. This phase 2, randomized, placebo-controlled, proof-of-concept study evaluated efficacy and safety of onfasprodil in patients with treatment-resistant major depression (TRD).

Methods: Adults with TRD who did not respond to ≥2 antidepressants were randomized (3:3:3:3:6:4) to receive a 40-minute intravenous infusion of onfasprodil 0.16 mg/kg weekly (n = 11), onfasprodil 0.16 mg/kg biweekly (n = 10), onfasprodil 0.32 mg/kg weekly (n = 10), onfasprodil 0.32 mg/kg biweekly (n = 9), placebo weekly (n = 20), or ketamine 0.5 mg/kg weekly (n = 10) for 6 weeks. Primary end point was change from baseline in Montgomery-Asberg Depression Rating Scale (MADRS) score at 24 hours. Secondary end points were change in MADRS score at 48 hours and at final follow-up at 6 weeks. Safety and tolerability were assessed during the study.

Results: Of 70 randomized patients, 53 (75.7%) completed the study. At 24 hours, adjusted mean differences versus placebo for pooled onfasprodil 0.16 mg/kg, 0.32 mg/kg, and ketamine groups were −8.25 ($P = .001$), −5.71 ($P = .019$), and −5.67 ($P = .046$), and at 48 hours, −7.06 ($P = .013$), −7.37 ($P = .013$), and −11.02 ($P = .019$), respectively. At Week 6, adjusted arithmetic mean MADRS difference between ketamine and placebo was −5.24 (80% CI, −10.42 to −0.06; $P = .0974$). At Week 6, the difference versus placebo on MADRS was −5.78 ($P = .0427$) for pooled 0.16 mg/kg and −4.24 ($P = .1133$) for pooled 0.32 mg/kg groups. The commonest treatment-emergent adverse events in the onfasprodil groups were dizziness (14.3%), transient amnesia (14.3%), and somnolence (11.4%). It had overall a good safety profile and was well tolerated.

Conclusion: Onfasprodil appeared to be effective and well-tolerated across all dosing regimens in patients with TRD and demonstrated rapid onset of action (24 hours) with evidence of antidepressant effects to be maintained at Week 6, particularly for the lower-dose group.

Trial Registration: ClinicalTrials.gov identifier: NCT03756129.

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Treatment-resistant depression (TRD) is defined as inadequate response to at least 2 different antidepressants for at least 6 weeks at an adequate dose.[1] About one-third of patients with major depressive disorder (MDD) do not respond to antidepressant treatment, and the majority does not maintain a long-term response to standard antidepressants and can be considered treatment-resistant.[2] There is a high unmet medical need for effective and well-tolerated rapid-acting antidepressants that can effectively end a depressive episode and prevent future depression.

Ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to be effective in TRD due to its rapid onset, and ability to reduce suicidality, and

Clinical Points

With the limitation of small sample sizes per subgroup arm, this proof of concept study demonstrates the following:

- Rapid onset of action of onfasprodil and sustained benefit with repeated dosing vs placebo, and efficacy similar to ketamine in a small subgroup, suggesting possible therapeutic utility in the treatment-resistant depression population.
- An overall good safety profile that was well tolerated.
- Greater efficacy at the lowest dose at the lowest frequency of onfasprodil vs other arms.

sustained benefit with repeated dosing,[3,4] but it is associated with reversible dissociative and psychotomimetic effects that sometimes can be severe.[5] Esketamine (nasal spray), an enantiomer of ketamine approved by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) for TRD, also shares these risks.

Traxoprodil (CP-101,606), a negative allosteric modulator (NAM) selective for the NR2B subtype of the NMDA receptor, was also effective in patients with TRD, with a magnitude and duration of response comparable to that of ketamine, but without producing a dissociative reaction at the lower dose infusion.[6] The development of traxoprodil was halted because of QTc prolongation.[7,8]

Onfasprodil (MIJ821), a highly potent and selective NMDA NR2B subunit NAM, is expected to exert a rapid antidepressant effect compared to traxoprodil and ketamine; therefore, it is intended to be studied in TRD. Onfasprodil has shown low rates of psychotomimetic side effects in a first-in-human study.[9] Hence, onfasprodil could be a potential treatment option for patients with TRD. We evaluated the efficacy and safety of onfasprodil in patients with TRD in a proof-of-concept study.

METHODS

Study Design

This was a phase 2, randomized, double-blind, placebo-controlled, parallel-group, multicenter study (ClinicalTrials.gov identifier NCT03756129) with 6 treatment arms conducted in Spain and with 5 treatment arms in the United States where the ketamine arm was not included. The total study duration was 14 weeks and comprised a screening period (maximum 4 weeks), a 36-day treatment period, and a 5-week follow-up period (Figure 1A).

Study Treatment and Randomization

Seventy patients were randomized (3:3:3:3:6:4) to one of the following treatment arms: onfasprodil 0.16 mg/kg 1 infusion per week from Day 1 to Day 36; onfasprodil 0.16 mg/kg 1 infusion biweekly on Day 1, Day 15, and Day 29 and placebo on Day 8, Day 22, and Day 36; onfasprodil 0.32 mg/kg 1 infusion per week from Day 1 to Day 36; onfasprodil 0.32 mg/kg 1 infusion biweekly on Day 1, Day 15, and Day 29 and placebo on Day 8, Day 22, and Day 36; placebo 1 infusion per week from Day 1 to Day 36; and ketamine 0.5 mg/kg, limiting dose at 40 mg/infusion for patients over 80 kg, 1 infusion per week from Day 1 to Day 36 (absence of the ketamine arm in the US). All study treatments were administered via a 40-minute intravenous infusion at the site. Based on preclinical rodent PET studies, both doses (0.16 and 0.32 mg/kg) were projected to give a maximum receptor occupancy greater than 90% of brain NR2B receptors (data on file).

Randomization was implemented using Interactive Response Technology, using a validated system that automated the random assignment of patient numbers to randomization numbers. Randomization was stratified by region, the United States, and European countries.

Study Population

The study enrolled adults (aged 18–65 years) with MDD and prior failure of ≥2 standard antidepressants (where 2 of the failed treatments were different antidepressants, at least 1 of which was being taken in the current depressive episode) of adequate dose and ≥8 weeks duration in a major depressive episode (per *DSM-5* criteria) and a Montgomery-Asberg Depression Rating Scale (MADRS) score ≥24.[10,11] Details of exclusion criteria are provided in Supplementary Appendix 1.

The study was conducted in accordance with ICH E6 Guideline for Good Clinical Practice as per the Declaration of Helsinki. Study protocol was reviewed and approved by the Independent Ethics Committee or Institutional Review Board for each center. All participants provided written informed consent before study initiation.

Study End Points and Assessments

The primary outcome was change from baseline in the MADRS total score at 24 hours after single-dose administration. The MADRS is a clinician-rated scale designed to measure depression severity and detect changes due to antidepressant treatment. The primary end point was analyzed using an analysis of covariance (ANCOVA) model with treatment as a group factor and baseline MADRS score as a covariate. The 2-sided 80% confidence intervals (CIs) and 1-sided *P* values were calculated for the treatment differences (each onfasprodil dose versus placebo). Other treatment comparisons (eg, ketamine versus placebo; ketamine versus onfasprodil pooled dose group) were also estimated from the described ANCOVA model; however,

the study was not formally powered for these comparisons.

The key secondary outcomes assessed were change from baseline in MADRS score at 48 hours after the first dose and at 6 weeks after repeated dose administration. In addition, the change from baseline in the total MADRS score was analyzed using the mixed-effects models for repeated measures (MMRM). The MMRM model included the fixed, categorical effects of treatment, time (at all planned time points, including but not limited to 24 hours, 48 hours after the first dose, and after the last dose [Day 36]), and treatment × time interaction, as well as the continuous, fixed covariates of baseline score, and baseline score × time interaction. Other secondary efficacy end points were analyzed using the MMRM approach, in the same way as the MADRS total score as described above.

Of particular interest were the dissociative effects, which were measured using the Clinical-Administered Dissociative States Scale (CADSS) questionnaire and the Dissociative Experiences Scale (DES) throughout the study.[12,13] Pharmacokinetics, safety, and tolerability were also assessed. Please see Supplementary Appendix 2 for detailed methodology and results of other secondary end points.

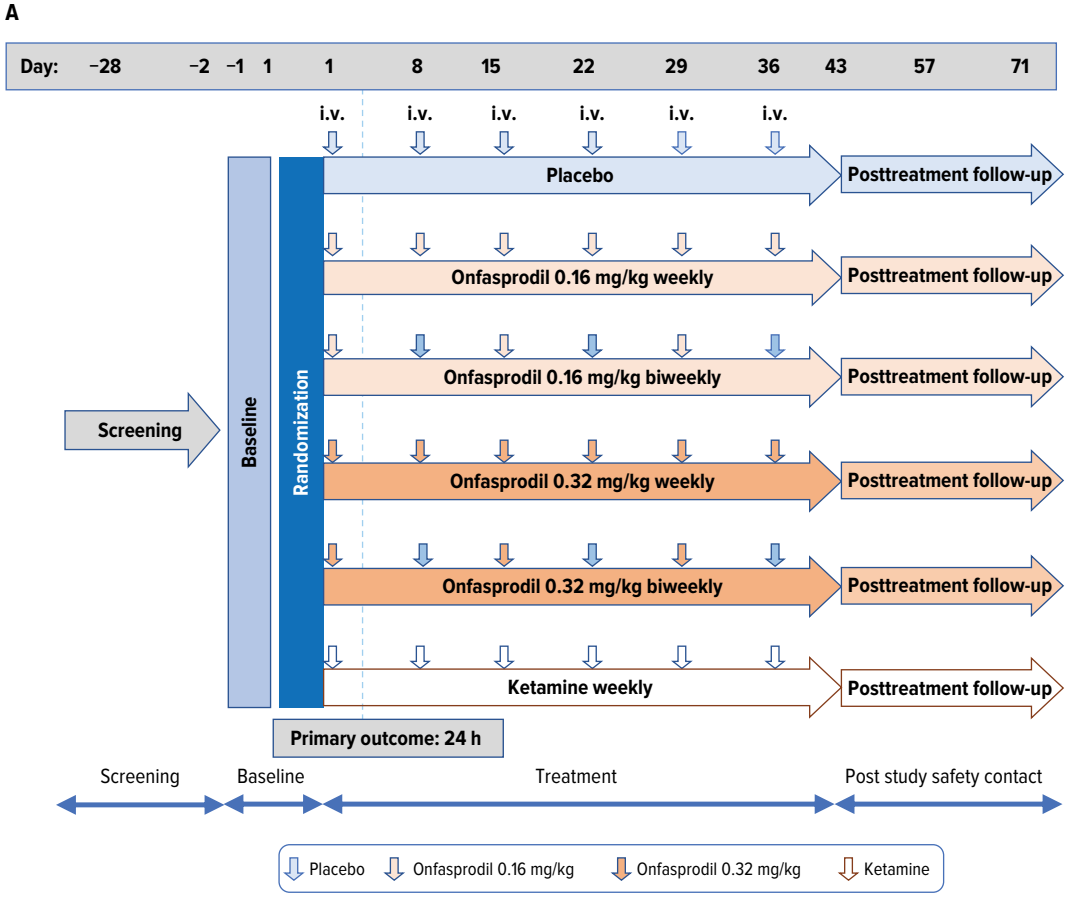
All the participants who received at least 1 dose of the study drug were evaluated for safety and adverse events (AEs) including dissociative AEs of interest such as dissociation (environmental perception disturbance or foggy thoughts), amnesia (memory loss), or AEs such as sedation and vomiting.

Please refer to Supplementary Appendix 3 for details of concomitant and prohibited medication.

Statistical Analysis and Sample Size Calculation

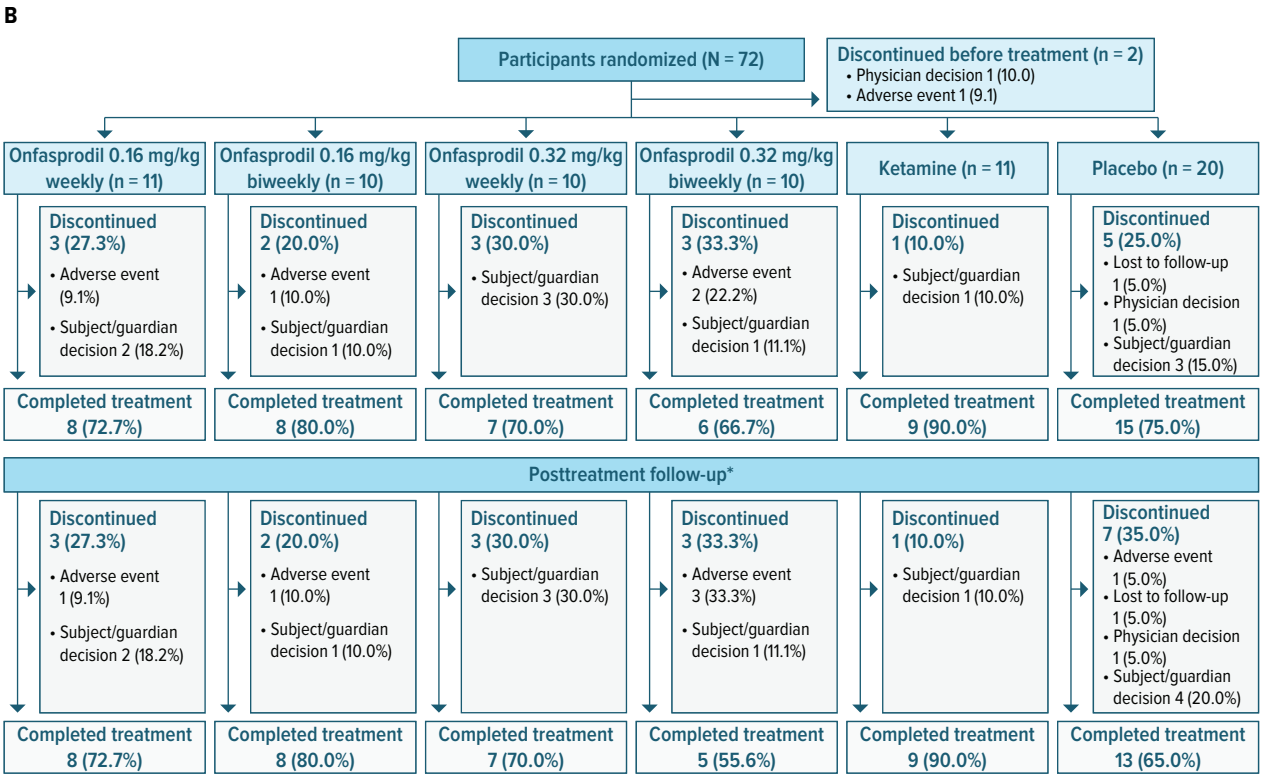
Data were analyzed using the analysis sets (see Supplementary Appendix 4). A sample size of 66 patients was planned to be randomized among 6 treatment groups in a 18:12:9:9:9:9 ratio (n = 18 placebo; n = 12 ketamine; n = 9 onfasprodil 0.16 mg/kg weekly; n = 9 onfasprodil 0.16 mg/kg biweekly; n = 9 onfasprodil

Figure 1.
(A) Study Design and (B) Trial Profile[a]



[a]Onfasprodil is also referred as MIJ821.
Abbreviation: IV = intravenous.

Figure 1.
(Continued).



0.32 mg/kg weekly; n = 9 onfasprodil 0.32 mg/kg biweekly), which was considered sufficient to achieve the trial objectives. The study investigated 2 primary comparisons at 24 hours after single-dose administration: onfasprodil 0.16 mg/kg vs placebo and onfasprodil 0.32 mg/kg vs placebo. Data from patients assigned to the same dose, but a different regimen were pooled for the purpose of treatment comparison. Based on prior data,[1] the standard deviation (SD) of change from baseline to 24 hours after start of first infusion in the total MADRS score was estimated to be 10 points. Assuming the true mean difference (onfasprodil minus placebo) as 8 points (standardized treatment effect size = 0.8), data from 18 evaluable patients per group would provide ~86% power to detect statistically significant treatment differences using 1-sided $\alpha = .10$.

RESULTS

Patient Disposition

Overall, 72 patients were randomized, with 2 patients discontinuing from the study before receiving study treatment (Figure 1B). Of the remaining 70 participants, 53 (75.7%) completed the study. The most common reason for discontinuing treatment was subject decision (11 [15.7%]). The mean (SD) age of patients treated in the study was 47.7 (11.3) years. A majority of the participants were White/European American (56%) or Black/African American (41%) (Table 1).

Primary End Point

The study met the primary outcome, a change from baseline in the MADRS total score at 24 hours after single-dose administration. Statistically significant and clinically relevant differences were observed between each of the onfasprodil groups (0.16 and 0.32 mg/kg) and placebo at 24 hours after start of infusion, and the efficacy was maintained in both pooled groups through 48 hours (Figure 2). The adjusted arithmetic mean difference between the onfasprodil 0.16 mg/kg group and the placebo group was −8.25 ($P = .0013$). The adjusted arithmetic mean difference between the onfasprodil 0.32 mg/kg group and the placebo group was −5.71 ($P = .0196$). At 24 hours after start of infusion, the ketamine treatment group had a statistically significant lower total MADRS score than the placebo treatment group (adjusted mean difference: −5.67, $P = .0461$) (Supplementary Table 1). At 48 hours after start of first infusion, a statistically significant decrease in the total MADRS score for both pooled onfasprodil groups and the ketamine group versus placebo was

Table 1.

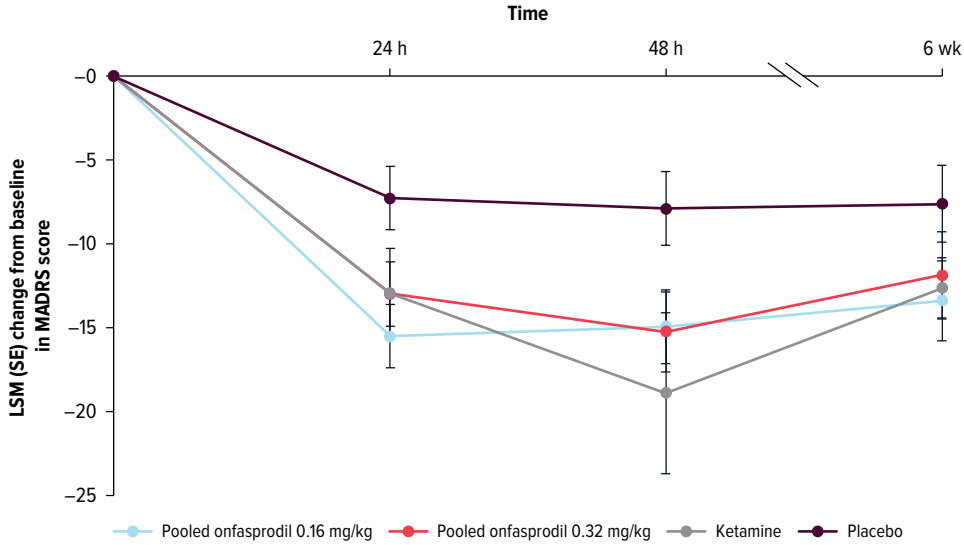
Baseline Demographic and Disease Characteristics[a]

	Onfasprodil, 0.16 mg/kg, weekly N = 11	Onfasprodil, 0.16 mg/kg, biweekly N = 10	Onfasprodil, 0.32 mg/kg, weekly N = 10	Onfasprodil, 0.32 mg/kg, biweekly N = 9	Pooled onfasprodil, 0.16 mg/kg N = 21	Pooled onfasprodil, 0.32 mg/kg N = 19	Ketamine N = 10	Placebo N = 20	Total N = 70
Age, y	48.6 (11.7)	53.7 (9.3)	42.9 (14.5)	46.6 (11.8)	51.0 (10.7)	44.6 (13.1)	52.3 (7.0)	44.8 (10.7)	47.7 (11.3)
Sex, n (%)									
Female	2 (18)	5 (50)	6 (60)	6 (67)	7 (33)	12 (63)	7 (70)	9 (45)	35 (50)
Male	9 (82)	5 (50)	4 (40)	3 (33)	14 (67)	7 (37)	3 (30)	11 (55)	35 (50)
Race, White, n (%)	8 (73)	6 (60)	6 (60)	1 (11)	14 (67)	7 (37)	9 (90)	9 (45)	39 (56)
BMI, kg/m²	32.6 (5.9)	29.7 (7.0)	31.3 (8.3)	29.9 (5.0)	31.2 (6.5)	30.7 (6.8)	26.8 (4.9)	28.9 (6.5)	29.8 (6.4)
MADRS total score	35.5 (6.7)	33.1 (5.3)	30.0 (5.4)	34.4 (6.5)	34.3 (6.0)	32.1 (6.2)	30.2 (4.9)	33.5 (5.3)	32.9 (5.8)
CGI-S total score	4.7 (0.8)	4.7 (0.8)	4.5 (0.7)	4.8 (0.4)	4.7 (0.8)	4.6 (0.6)	4.7 (1.0)	4.7 (0.6)	4.7 (0.7)
BRMS total score	23.7 (5.8)	20.1 (6.1)	18.2 (5.2)	21.7 (4.0)	22.0 (6.1)	19.8 (4.9)	21.9 (4.7)	21.6 (4.0)	21.3 (5.0)
CORE total score	12.5 (11.6)	3.3 (4.2)	10.0 (8.4)	18.0 (8.9)	8.6 (9.9)	13.4 (8.9)	13.1 (9.1)	14.4 (7.9)	12.6 (8.7)
KMDRS total score	5.3 (3.7)	6.8 (3.1)	4.1 (2.2)	5.9 (1.9)	6.0 (3.5)	4.9 (2.2)	7.4 (4.6)	6.4 (3.9)	6.0 (3.5)
HAS total score	15.0 (6.2)	14.0 (5.0)	11.3 (5.5)	15.0 (5.6)	14.5 (5.5)	13.1 (5.7)	15.1 (3.3)	14.1 (5.2)	14.1 (5.2)
YMRS total score	3.4 (2.5)	4.9 (2.4)	2.4 (1.9)	4.3 (1.6)	4.1 (2.5)	3.3 (2.0)	1.8 (1.3)	3.4 (2.2)	3.3 (2.2)
Sheehan-STS total score	0.5 (0.8)	0.5 (0.9)	0.3 (0.7)	0.6 (1.1)	0.5 (0.8)	0.4 (0.9)	0.5 (1.3)	0.4 (0.7)	0.4 (0.9)

[a]Data are presented as mean (SD) unless specified.
Abbreviations: BMI = body mass index, BRMS = Bech-Rafaelsen Melancholia Scale, CGI-S = Clinical Global Impression-Severity, HAS = Hamilton Anxiety Scale, KMDRS = Koukopoulos Mixed Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, SD = standard deviation, Sheehan-STS = Sheehan-Suicidality Tracking Scale, YMRS = Young Mania Rating Scale.

Figure 2.

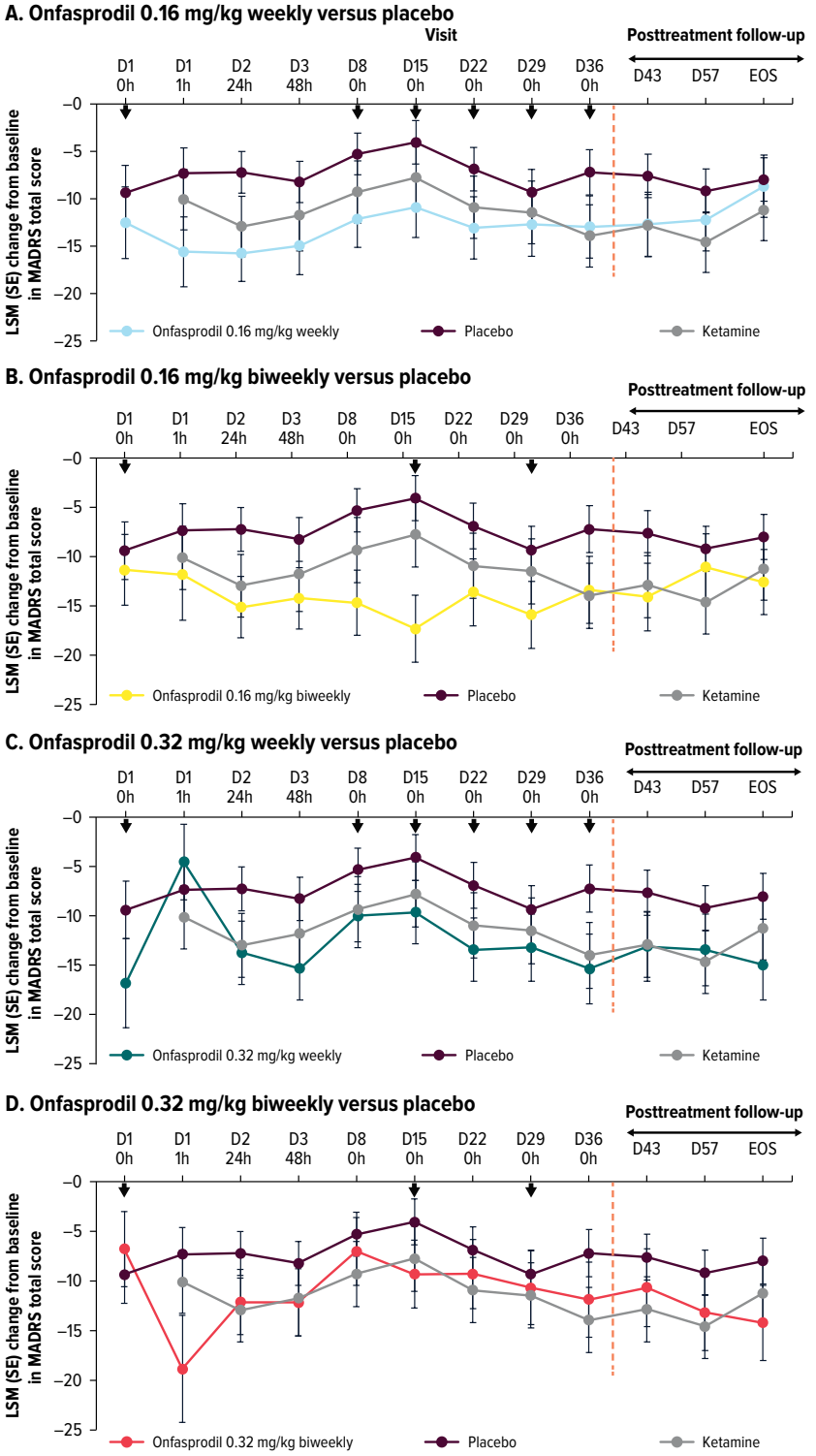
ANCOVA-Based Mean Change from Baseline in the Total MADRS Score (ITT Analysis Set)[a,b]



[a]Baseline is defined to be the last available measurement obtained before the first infusion on Day 1. The total MADRS scores at 24 h and 48 h were recorded after the first infusion, and the 6-wk measurement was collected 1 wk after the last infusion. The change from baseline in the total MADRS score at 6 wk was analyzed using MMRM. The model includes the fixed, categorical effects of treatment, time (at all planned postbaseline time points and not restricted at Week 6) and treatment × time interaction, as well as the continuous, fixed covariates of baseline score, and baseline score × time interaction. An AR(1) structure was used to model the within-subject errors.
[b]Onfasprodil is also referred as MIJ821.
Abbreviations: ANCOVA = analysis of covariance, AR(1) = first-order autoregressive, h = hours, ITT = intent to treat, LSM = least-squares mean, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed-effects models for repeated measures, SE = standard error.

Figure 3.

MMRM Least-Squares Means (SE) Change From Baseline in Total MADRS Score[a]



[a]Onfasprodil is also referred as MIJ821. Downward-pointing arrows indicate dosing days for onfasprodil; vertical dotted lines indicate end of treatment at Day 36.

Abbreviations: D = day, EOS = end of study, h = hours, LSM = least-squares mean, MADRS = Montgomery-Asberg Depression Rating Scale, MMRM = mixed model repeated measures, SE = standard error.

maintained. The magnitude of mean decreases in the total MADRS score in the onfasprodil groups (pooled onfasprodil 0.16 mg/kg: −14.94; pooled onfasprodil 0.32 mg/kg: −15.25) was less pronounced than that observed in the ketamine group (−18.89), but the difference between the onfasprodil groups and ketamine was not statistically significant (Figure 2; Supplementary Table 2).

Secondary Efficacy Results

At Week 6 (Day 43 in Figure 3; see also Supplementary Table 3), there was a statistically significant ($P < .10$) decrease in the total MADRS score for 2 of the 4 onfasprodil treatment groups: onfasprodil 0.16 mg/kg biweekly group (Figure 3B) and onfasprodil 0.32 mg/kg weekly group (Figure 3C) versus the placebo group. On MMRM analysis, the adjusted arithmetic mean difference (80% CI; *P* value) between the onfasprodil 0.32 mg/kg weekly treatment group and the placebo treatment group was −5.42 (−10.83 to −0.02; $P=.0993$), and between the onfasprodil 0.16 mg/kg biweekly treatment group and placebo, it was −6.46 (−11.78 to −1.15; $P = .0598$) (Supplementary Table 4). Thus, the onfasprodil 0.16 mg/kg biweekly group demonstrated the greatest overall MADRS benefit compared with placebo.

The pharmacokinetic methods and results are presented in Supplementary Appendix 5. The Supplementary Figure 1 showed plasma onfasprodil concentrations over time after the first infusion.

Safety

The CADSS total score in the placebo treatment group was low and remained stable throughout the study (Supplementary Table 5). The CADSS total score for the onfasprodil 0.16 mg/kg weekly and biweekly treatment groups was greater than baseline values from the end of the first infusion up to 24 hours after start of infusion, and up to 48 hours after start of infusion for the onfasprodil 0.32 mg/kg weekly and biweekly treatment groups. In the ketamine treatment group, the CADSS total score reached the peak value at 1 hour after the start of infusion (mean change from baseline: 10.30) and then returned to baseline level at 24 hours after the start of infusion.

The DES total score was relatively low in each treatment group and was stable throughout the study, except for higher values in the onfasprodil 0.32 mg/kg biweekly treatment group from baseline to 24 hours after the start of infusion.

At 24 hours, 48 hours, and Week 6 after the start of first infusion, the median score for both the Sheehan-Suicidality Tracking Scale (STS) suicidal behavior subscale and the Sheehan-STS suicidal ideation subscale was 0 in each treatment group.

The incidence of both overall AEs and treatment-emergent AEs (TEAEs) among the onfasprodil-treated groups and the ketamine treatment group was higher than in the placebo treatment group. The proportion of patients who reported at least 1 AE in the pooled onfasprodil 0.16 mg/kg and pooled onfasprodil 0.32 mg/kg was 61.9% (13/21) and 68.4% (13/19), compared to 60.0% (6/10) in the ketamine and 35.0% (7/20) in the placebo group, respectively (Table 2). Most of the AEs were mild in intensity. Moderate and severe AEs were reported in 18.6% and 14.3% of patients, respectively (see Supplementary Table 6; see Supplementary Tables 7–9 for more details on the incidence of AEs by system organ class, preferred terms, and incidence of AEs of interest). One patient in the onfasprodil 0.32 mg/kg biweekly treatment group had a life-threatening AE (suicidal threat), which was not considered to be related to the study treatment.

Treatment-emergent AEs were reported in 45.5% (5/11) of patients in the onfasprodil 0.16 mg/kg weekly group, 50.0% (5/10) of patients in the onfasprodil 0.16 mg/kg biweekly group, 70.0% (7/10) of patients in the onfasprodil 0.32 mg/kg weekly group, and 55.6% (5/9) of patients in the onfasprodil 0.32 mg/kg biweekly group, compared to 60.0% (6/10) of patients in the ketamine group and 25.0% (5/20) of patients in the placebo group. The most common TEAEs (>10%) reported among the onfasprodil-treated groups included dizziness, amnesia, somnolence, and feeling abnormal (Table 3). The most common side effects with ketamine were depersonalization/derealization, dry mouth, and dizziness.

The maximum time to onset of significant AEs was 4.4 hours after the start of infusion in patients treated with onfasprodil (sedation) (Supplementary Table 10). All the TEAEs of interest were resolved within a few hours after onset. The maximum time to resolution after the onset of AE was 9.2 hours in patients treated with onfasprodil (Supplementary Table 11). Short periods of amnesia were reported in 10 patients treated with onfasprodil; the time to onset ranged from 0 to 0.7 hours after start of infusion, and the time to resolution ranged from 0.7 to 9.2 hours after onset. Dissociation was reported in 10 patients treated with onfasprodil (5 [23.8%] in the pooled onfasprodil 0.16 mg/kg group and 5 [26.3%] in the pooled onfasprodil 0.32 mg/kg group); the time to onset ranged from 0 to 0.7 hours after the start of infusion, and the time to resolution ranged from 1.6 to 7.0 hours after onset. In the ketamine group, dissociation was reported in 5 (50.0%) patients, the time to onset ranged from 0.1 to 0.2 hours after the start of infusion, and the time to resolution ranged from 0.8 to 2.3 hours after onset.

Table 2.

Incidence of AEs of Interest (Safety Analysis Set)

	Pooled onfasprodil, 0.16 mg/kg N = 21	Pooled onfasprodil, 0.32 mg/kg N = 19	Ketamine N = 10, n (%)	Placebo N = 20, n (%)
Patients with at least 1 AE	13 (61.9)	13 (68.4)	6 (60.0)	7 (35.0)
AEs of interest				
Amnesia	2 (9.5)	8 (42.1)	0	0
Dissociation	5 (23.8)	5 (26.3)	5 (50.0)	2 (10.0)
Dissociation and amnesia	2 (9.5)	1 (5.3)	0	0
Sedation	3 (14.3)	4 (21.1)	1 (10.0)	0
Vomiting	0	1 (5.3)	0	0

Abbreviation: AE = adverse event.

Table 3.

Incidence of AEs (≥2 Patients in Any Treated Group) by Preferred Term (Safety Analysis Set)[a]

	Onfasprodil, 0.16 mg/kg weekly N = 11, n (%)	Onfasprodil, 0.16 mg/kg biweekly N = 10, n (%)	Onfasprodil, 0.32 mg/kg weekly N = 10, n (%)	Onfasprodil, 0.32 mg/kg biweekly N = 9, n (%)	Ketamine N = 10, n (%)	Placebo N = 20, n (%)
Patients with at least 1 AE	7 (63.6)	6 (60.0)	7 (70.0)	6 (66.7)	6 (60.0)	7 (35.0)
Amnesia	2 (18.2)	0	5 (50.0)	3 (33.3)	0	0
Dizziness	2 (18.2)	3 (30.0)	1 (10.0)	1 (11.1)	2 (20.0)	1 (5.0)
Feeling abnormal	3 (27.3)	1 (10.0)	2 (20.0)	0	0	0
Headache	1 (9.1)	0	2 (20.0)	1 (11.1)	1 (10.0)	1 (5.0)
Somnolence	2 (18.2)	1 (10.0)	4 (40.0)	0	1 (10.0)	0
Fatigue	0	0	2 (20.0)	1 (11.1)	1 (10.0)	1 (5.0)
Dry mouth	0	0	0	0	3 (30.0)	1 (5.0)
Nausea	0	1 (10.0)	1 (10.0)	0	2 (20.0)	0
Ataxia	0	0	1 (10.0)	2 (22.2)	0	0
Blood pressure increased	2 (18.2)	1 (10.0)	0	0	0	0
Confusional state	0	0	1 (10.0)	1 (11.1)	0	1 (5.0)
Dissociation	2 (18.2)	0	0	0	0	1 (5.0)
Depersonalization/ derealization	0	0	0	0	5 (50.0)	0
Insomnia	2 (18.2)	0	0	0	0	1 (5.0)
Memory impairment	2 (18.2)	0	1 (10.0)	0	0	0
Hyperacusis	0	0	0	0	2 (20.0)	0

[a]Only AEs occurring from the date of first administration of study treatment to 30 d after the date of the last actual administration of any study treatment are included.
Abbreviations: AE = adverse event, N = number of patients studied, n = number of patients with at least 1 AE in the category.

Serious AEs, including asthma, atrial fibrillation, depression, suicide threat, and suicide attempt, were reported in 5 patients (7.1%): 1 in the onfasprodil 0.16 mg/kg biweekly group, 3 in the onfasprodil 0.32 mg/kg biweekly group, and 1 in the placebo group. None were considered related to the study treatment. Four patients discontinued the study treatment due to AEs, 1 in the onfasprodil 0.16 mg/kg weekly group (blood potassium decreased, alanine aminotransferase [ALT] increased, aspartate aminotransferase [AST] increased, and γ-glutamyl transferase increased), 2 in the onfasprodil 0.32 mg/kg biweekly group (atrial fibrillation and major depression), and 1 in the placebo group (suicidal ideation). No deaths were reported in the study.

DISCUSSION

This study is the first randomized clinical trial that assesses the potential efficacy of a novel NR2B selective negative allosteric modulator, onfasprodil (MIJ821), versus placebo, showing benefit at 24 hours and 48 hours, and persisting up to 6 weeks at lower doses. In a small subgroup, it also compared this agent to the standard NMDA receptor blocker, ketamine, with similar apparent efficacy results. This comparison provides initial data on relative efficacy and safety of this novel agent compared with the most commonly used NMDA receptor inhibitors currently available for clinical care. This proof-of-concept trial demonstrates

onfasprodil may be effective for the rapid reduction of depressive symptoms in patients with TRD, with mild dissociative side effects that resolve rapidly. Onfasprodil showed a significantly improved MADRS total score at 24 hours after start of infusion compared with placebo, and efficacy was maintained at 48 hours. The largest and the most consistent benefit versus placebo was observed with the lower dose onfasprodil 0.16 mg/kg biweekly treatment regimen, the effects of which lasted at least 2 weeks.

In this study, the difference between onfasprodil-treated groups and placebo was 5 points or more, which is considered a clinically relevant difference in change in depression.[14,15] Onfasprodil demonstrated greater improvements than placebo (0.16 mg/kg pooled group: 8.25-point greater reduction versus placebo) in the MADRS total score at 24 hours. While comparisons across different trials should be done with caution, due to different samples and different methods, the effect size difference between onfasprodil and placebo in this study was consistent with a prior study with a drug with a similar mechanism, traxoprodil (CP101,606) (8.4-point greater reduction versus placebo),[6] and prior phase 2 trials of high dose of esketamine (esketamine 84 mg [both periods combined]: 9.0-point greater reduction versus placebo).[16]
These effect sizes differ from the smaller drug versus placebo effect sizes (2–4 points on MADRS) seen in most studies of selective serotonin reuptake inhibitors[17] and phase 3 esketamine trials.[18] The rapid onset of action and continued numerical benefit in total MADRS score at Week 6 suggests that onfasprodil may bridge the efficacy gap created by the delayed onset of action of standard antidepressants.

This study employed a less stringent 1-tailed *P* value than the typical 2-tailed *P* value that is more commonly seen in registration trials. The reason for this is that this was a proof-of-concept trial for the purpose of the determining if further development is warranted and at what dose and frequency. This is why 2 doses (0.16 and 0.32 mg/kg) at 2 frequencies each (weekly and biweekly) were employed. Using a 1-tailed *P* value is not unusual in early-stage clinical trials given that sample sizes are usually low and only 1 outcome is meaningful.[2] In this case, the only meaningful outcome is if 1 or more doses and frequencies separate from placebo. As noted by Dahlberg et al, "(a) threshold of 0.05 is thought to be the conventional type I error rate; but in fact, the origin of this threshold is arbitrary, and in practice designs often have lower or higher false-positive thresholds depending on design features such as…phase of development."[3] Two-sided *P* values will be used in future registration trials should they occur.

In the present study, although most patients had low scores in the MADRS suicidal category at baseline, a reduction in suicidal ideation item of the MADRS was seen immediately after the first dose of each study treatment, which remained steady throughout the study with no increased risk. Therefore, onfasprodil may have the potential to improve suicidal symptoms, and further studies in MDD patients with serious suicidal ideation are needed to determine short- and long-term benefits, an effect that is consistent with literature reports for ketamine and esketamine.[19–21]

Similar to other NR2B-selective antagonists,[22] the pharmacodynamic effects of onfasprodil appear to be sustained beyond the level and duration of drug exposure indicated by the pharmacokinetic parameters. While the half-life of onfasprodil is approximately 7 hours, clinical efficacy was maintained for up to 2 weeks. Interestingly, previous studies have shown ketamine and Ro 25-6981 (another NMDA NR2B NAM like onfasprodil) can demonstrate effects on protein synthesis and synaptogenesis.[23]

Ketamine is a nonselective NMDA receptor blocker that can produce significant adverse effects including dissociative and psychomimetic effects. The data with onfasprodil indicate a favorable safety and tolerability profile with few patients discontinuing due to TEAEs. This tolerability may be attributable to the NMDA receptor subtype selectivity and mechanism of action of this class of molecules.[24,25]

The most frequently reported treatment-related AEs with onfasprodil were dizziness, amnesia, and somnolence. Dissociative-type side effects were mild with onfasprodil. The maximum increase in CADSS total score was higher in the ketamine group (mean maximum change from baseline was 10.30) than in the onfasprodil treatment groups (mean maximum change from baseline: ≤5).

Of note, all the treatment-related AEs of interest resolved within a few hours after onset, and there were no clinically relevant changes in clinical laboratories, vital signs, or ECGs. Overall, onfasprodil was well tolerated across all dosing regimens.

Several limitations of the study should be considered in the interpretation of the findings. The sample size was relatively small, and the trial was conducted in a limited number of research sites. The dropout rate in the acute treatment phase ranged from 10% in the ketamine group to 33.3% in the onfasprodil 0.32 mg/kg weekly groups. Ketamine was administered only once per week and how this compares to the more standard twice-weekly initial dosing is unknown. Ketamine was also administered at a fixed dose rather than the more customary 0.5 mg per kg over 40 minutes. Therefore, the plasma concentrations might have been lower for some patients with higher body mass indexes. Nonetheless, there was a statistically significant and clinically meaningful difference between ketamine and placebo. A greater difference might have been achieved with more conventional dosing. However, a significant difference between ketamine and placebo

assured sufficient assay sensitivity, ensuring that the study was internally valid.

Despite the small sample size, this proof-of-concept study suggests that selected dosing regimens of onfasprodil may be effective and well-tolerated in patients with TRD, with rapid onset of action (24-hours) with evidence of antidepressant effects to be maintained at Week 6, particularly for the lower-dose group. Further studies with larger sample sizes are necessary to confirm these preliminary findings.

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Supplementary Material

Article Title: Rapid Onset and Sustained Efficacy of Onfasprodil (MIJ821), a Novel NR2B Negative Allosteric Modulator, in Patients with Treatment-Resistant Depression: A Phase 2, Randomized, Placebo-Controlled, Proof-of-Concept Study

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

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13. **Table 8**
14. **Table 9**
15. **Table 10**
16. **Table 11**
17. **Figure 1**

DISCLAIMER

Supplementary material

Supplementary Appendix 1

Exclusion criteria

To summarise, participants were excluded if they had bipolar disorder, schizophrenia, or schizoaffective disorder, borderline personality disorder or antisocial personality disorder, acute depressive episode lasting longer than 2 years continuously, acute serious and/or imminent suicidal ideation and/or intent within the previous 2 weeks, or any suicide attempt within the previous 4 weeks at screening. In addition, those with alcohol or substance use disorder (including marijuana and prescribed amphetamine) meeting DSM-5 criteria, use of other investigational drugs within 30 days or 5 half-lives prior to randomization (whichever was longer) at baseline were excluded from the study (see below for complete list of exclusion criteria).

List of exclusion criteria

1. Any current diagnosis of bipolar disorder, schizophrenia, or schizoaffective disorder at screening.
2. Current alcohol or substance use disorder (including marijuana and prescribed amphetamine) meeting DSM-5 criteria, within the past month at baseline.
3. Prior suicidality caused by or associated with ketamine.
4. Acute serious and/or imminent suicidal ideation and/or intent within the prior 2 weeks, or any suicide attempt within the prior 4 weeks at screening.
5. Use of other investigational drugs within 30 days or 5 half-lives prior to randomization, whichever was longer; or longer if required by local regulations at baseline.
6. Pregnant or nursing (lactating) women or women of childbearing potential.
7. Positive HIV, Hepatitis B or C test.

8. Resting QTcF ≥ 450 msec (male) or ≥ 460 msec (female) at pre-treatment baseline.

9. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer) within 3 years prior to screening.

10. Sexually active males unwilling to use a condom during intercourse while taking investigational drug and for 1 week after stopping study treatment.

11. History of hypersensitivity to any of the study treatments or excipients or to drugs similar to chemical classes that affect NMDA receptor.

12. Current diagnosis of borderline personality disorder or antisocial personality disorder, based on DSM-5 criteria.

13. Current acute depressive episode lasting longer than 2 years continuously

Supplementary Appendix 2

Montgomery Åsberg Depression Rating Scale

Montgomery Åsberg Depression Rating Scale (MADRS) is a clinician-rated scale designed to measure depression severity and detects changes due to antidepressant treatment: the test consists of 10 items, each of which is scored from 0 (item not present or normal) to 6 (severe or continuous presence of the symptoms), for a total possible score of 60. Higher scores represent a more severe condition (Muller MJ et al. 2023).

Clinical-Administered Dissociative States Scale

Clinical-Administered Dissociative States Scale (CADSS) (Bremner JD et al. 1998) is a questionnaire that assesses dissociative effects. Each item is scored from 0 to 4 and individual scores are to be summed to obtain a total score ranging from a minimum of 0 to a maximum of 80. Higher scores represent a more severe condition.

Dissociative Experiences Scale

Dissociative Experiences Scale (DES) (Bernstein and Putnam 1986) consists of 28 questions about experiences the patients have had in their daily life. The patient determines to what degree they have been facing the situation by selecting a percentage from 0% (never) to 100% (always), with 10% increments in between. Higher scores mean higher severity.

Other secondary endpoints

Other secondary outcomes included the percentage treatment response (>50% improvement in MADRS), percentage treatment remission (MADRS <7), change from baseline in total Clinical Global Impression – severity (CGI-S) score, total CGI-improvement (CGI-I) score, total Young Mania Rating scale (YMRS) score, total Bech-Rafaelsen Melancholia Scale [BRMS] score, total CORE Melancholia scale score, total Koukopoulos Mixed Depression

Rating Scale (KMDRS) score, total Hamilton Anxiety Scale (HAS) score, and suicidal thoughts by the Sheehan-Suicidality Tracking Scale (Sheehan-STS) were measured. In addition, regression model effect sizes (odds ratios) for HAS, BRMS, and KMDRS as predictors, with MADRS treatment response as the outcome at 24 hours, 48 hours, and 6 weeks after the start of the first infusion were evaluated.

The proportion of responders (patients with >50% improvement in MADRS score) and the proportion of treatment remissions (subjects with MADRS < 7) were analyzed separately, using a logistic regression model that included the fixed, categorical effects of treatment, time, treatment-by-time interaction, the fixed continuous baseline MADRS score, and a random subject effect. The odds ratios quantifying differences between onfasprodil doses and placebo at different time points (with 90% CIs) were reported.

The CGI is a 3-item observer-rated scale, which measures the severity of symptoms, treatment response, and the efficacy of treatments in treatment studies of patients with mental disorders (Guy W 1976). CGI provides an overall clinician-determined summary measure that considers all available information, including a knowledge of the patient's history, psychosocial circumstances, symptoms, behavior, and the impact of the symptoms on the patient's ability to function. In this study two items were used: the CGI-Severity, which rates illness severity, and the CGI-Improvement, which rates change from the initiation of treatment.

The risk of mania induction was measured using the YMRS at 24 hours, 48 hours, and 6 weeks after the start of first infusion. The YMRS has 11 items and is based on the patient's subjective report of his/her clinical condition over the previous 48 hours after start of infusion. There are 4 items that are scored from 0 to 8 (irritability, speech, thought content, and

disruptive/aggressive behavior) and the remaining items are scored from 0 to 4 (Young RC 1978).

The efficacy of onfasprodil in the melancholic subtype of depression (measured by the BRMS and CORE Melancholia scale at 24 hours, 48 hours, and 6 weeks after the start of first infusion. BRMS scale is a clinician rating scale that emphasizes melancholic symptoms of depression over the past 3 days (Bech et al 1975). Each of the 11 BRMS items is operationally defined on a five-point scale (0–4); hence, the total score ranges from 0 to 44, higher scores indicating greater severity of depression. CORE scale is an 18-item scale, with a 6-item component capturing cognitive impairment and two motoric scales capturing psychomotor retardation (7 items) and psychomotor agitation (5 items). A cut-off score of 8 or more has been shown to differentiate melancholic from non-melancholic depression, with higher scores representing a greater probability of melancholic depression (Parker and McCraw 2017).

The efficacy on mixed mood symptoms was assessed by the KMDRS, on anxiety symptoms by HAS, and on suicidality by Sheehan-STS changes at 24 hours, 48 hours, and 6 weeks after the start of first infusion. The KMDRS assesses the excitatory or mixed nature in patients suffering from a Major Depressive Episode (MDE) as defined by DSM-5 criteria. The scale contains 14 items to be evaluated by clinical assessment and patient interview on symptoms potentially experienced over the past week. Overall score increases with severity of symptoms and has a maximum score of 51 (Sani G et al 2018). Hamilton anxiety scale measures psychic anxiety and somatic anxiety symptoms based on a clinical assessment and patient interview. The scale has 14 items, with each item rated from 0–4, ranging from not present to very severe. A maximum score of 56 indicates the most severe case (Hamilton M 1959). The Sheehan-STS is a sensitive psychometric tool to prospectively assess treatment-emergent suicidal thoughts and behaviors. The Sheehan-STS is a 14-item (up to 22) scale that

was administered by a clinician. Each item was scored on a 5-point Likert scale (0=not at all, 1=a little, 2=moderately, 3=very, and 4=extremely).

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Results

A greater proportion of patients in the four onfasprodil-treated groups and the ketamine group achieved a >50% improvement in MADRS at 24 hours, 48 hours, and Week 6 after the start of first infusion compared with the placebo group. The onfasprodil 0.32 mg/kg weekly treatment group had the highest responder rate (24 hours after start of first infusion: 50.0%; 48 hours after start of first infusion: 55.6%; Week 6: 50.0%) versus placebo (24 hours: 15.0%; 48 hours: 15.8%; Week 6: 11.8%). The odds ratio of reaching a >50% response at any time after the first infusion of any dose of onfasprodil or ketamine versus placebo was 2.76 (90% CI: 1.94 to 3.92).

At 24 hours, 48 hours, and 6 weeks after the first infusion, the proportion of patients who achieved treatment remission (MADRS <7) was, respectively, onfasprodil 0.16 mg/kg weekly: 9.1%, 22.2%, and 25.0%; onfasprodil 0.16 mg/kg biweekly: 20.0%, 10.0%, and 37.5%; onfasprodil 0.32 mg/kg weekly: 0, 11.1%, and 0; onfasprodil 0.32 mg/kg biweekly: 11.1%, 28.6%, and 16.7%; ketamine: 20.0%, 25.0%, and 22.2%; and placebo: 5.0%, 10.5%, and 11.8%.

On the CGI-S scale from baseline to Week 6, the proportion of patients whose condition was rated as “markedly ill” or “severely ill” decreased in each treatment group, and the magnitude of the decrease was numerically similar or higher in the onfasprodil treatment groups compared with the placebo treatment group (onfasprodil 0.16 mg/kg weekly: from 54.5% to 25.0%; onfasprodil 0.16 mg/kg biweekly: from 50.0% to 25.0%; onfasprodil 0.32 mg/kg weekly: from 40.0% to 12.5%; onfasprodil 0.32 mg/kg biweekly: from 77.8% to 33.3%; ketamine: from 40.0% to 22.2%; placebo: from 60.0% to 35.3%).

As measured by the CGI-I scale at 24 hours, 48 hours, and Week 6 after the first infusion, the proportion of patients whose condition was “very much improved” or “much improved” in each of the four onfasprodil treatment groups was higher than the ketamine treatment group and the placebo treatment group. The percentages at these three time points were as follows: onfasprodil 0.16 mg/kg weekly: 45.5%, 44.4%, and 37.5%; onfasprodil 0.16 mg/kg biweekly: 40.0%, 30.0%, and 50.0%; onfasprodil 0.32 mg/kg weekly: 50.0%, 44.4%, and 25%; onfasprodil 0.32 mg/kg biweekly: 33.3%, 28.6%, and 50.0%; ketamine: 10%, 25%, and 22.2%; and placebo: 10%, 10.5%, and 17.7%**,** respectively.

During the study, the total YMRS score did not increase in any treatment group.

In each treatment group, a reduction was observed in the total BRMS score following the first dose of study treatment; the magnitude of the reduction was similar in all treatment groups and remained relatively steady throughout the study, except for a greater reduction in the onfasprodil 0.16 mg/kg weekly treatment group at earlier time points (**Supplementary Table 2)**. The odds ratio of reaching >50% improvement in BRMS at any time after the first infusion of any dose of onfasprodil or ketamine versus placebo was 1.651 (90% CI: 1.20, 2.27).

Following the first dose of each study treatment, the total CORE Melancholia scale score was reduced versus placebo; the magnitude of the reduction was similar in all treatment groups and remained relatively constant throughout the study, except for some fluctuations in the onfasprodil 0.32 mg/kg biweekly treatment group (**Supplementary Table 2).**

Most patients did not have clinically significant suicidal ideation (this being an exclusion criterion during the study), with a score of less than 2 in the MADRS Suicidal Thoughts category. In the overall population, at baseline, patients had a mean score of 0.8 for suicidal ideation. The mean score in all treatment group decreased immediately after the first dose of

study treatment and remained steady throughout the study (**Supplementary Table 2)**. The mean change (range) from baseline at Week 6 after the first infusion was −0.8 (1.581) for onfasprodil 0.16 mg/kg weekly, −0.5 (0.756) for onfasprodil 0.16 mg/kg every other week, −0.3 (1.581) for onfasprodil 0.32 mg/kg weekly, −0.7 (1.633) for onfasprodil 0.32 mg/kg every other week, −0.2 (1.787) for ketamine, −0.2 (0.951) for placebo. The total patient population's mean change from baseline at Week 6 was −0.4 (1.315).

A reduction in total KMDRS score was observed following the first dose of each study treatment. The magnitude of reduction was relatively small and similar in all the treatment groups (**Supplementary Table 2**).

The mean score in total HAS was decreased at Day 22 predose and Week 6 compared to baseline, and the extent of the reduction was similar in all the treatment groups (**Supplementary Table 2)**.

Logistic regression analyses performed to evaluate the association between MADRS treatment response (>50% improvement) and KMDRS, BRMS and HAS showed that patients with lower scores in BRMS and HAS scales had higher probability to achieve MADRS treatment response.

Supplementary Appendix 3

Concomitant and Prohibited medication

All medications, procedures, and non-drug therapies initiated after study enrollment were recorded as concomitant medication. Agents that inhibit/induce CYP2D6, CYP2C19, and CYP2C8 were allowed but carefully monitored, and onfasprodil and concomitant medications were not administered at the same time. No new psychotropic drug was allowed after baseline.

Supplementary Appendix 4

Full analysis set

FAS comprised of all randomized patients who received at least 1 dose of study drug after randomization.

Intent-to-treat set

ITT set included all patients in the FAS who had received at least the first infusion on Day 1 and had at least 1 post-baseline efficacy measurement.

Pharmacokinetic analysis set

PK analysis set was defined as patients with at least one available valid (non-flagged for exclusion) PK concentration measurement, who received any study drug and experienced no protocol deviations with impact on PK data.

Safety analysis set

SAS included all patients who received at least 1 dose of study drug.

Supplementary Appendix 5

Pharmacokinetics

The pharmacokinetic (PK) properties of onfasprodil were described by maximum plasma concentration (C_{max}), time to reach C_{max} (T_{max}), area under the plasma concentration-time curve during a 24-hour period ($AUC_{0\text{-}24h}$) and AUC from time zero to the time of last measurable concentration (AUC_{last}). Plasma samples for PK analysis were collected at five time points (predose, end of infusion, 4, 24, and 48 hours after the start of infusion) for Day 1 dosing and two time points (predose and end of infusion) for Day 29 dosing. Data from patients assigned to the same dose but a different regimen were pooled into one treatment group for PK analysis, since the dosing regimen (weekly or biweekly) did not have an impact on the PK parameters after the first dose. The PK analysis was performed in all patients with at least one available valid PK concentration measurement and those who received any study drug and experienced no protocol deviations with an impact on PK data. The PK parameters (C_{max}, $AUC_{0.24\ h}$, AUC_{last}) were analyzed using descriptive statistics.

Results

Following the first infusion, the median T_{max} occurred at the end of infusion was 0.683 hours at 0.16 mg/kg and 0.667 hours at 0.32 mg/kg. Plasma onfasprodil concentrations over time after the first infusion are presented in **Supplementary Figure 1**. The C_{max} and AUC_{last} values of Onfasprodil increased in a less than dosage-proportional manner after the first infusion, and there was some overlap of the exposure parameters in between the two dose levels. For pooled 0.16 mg/kg and pooled 0.32 mg/kg, respectively, the $AUC_{0\text{-}24\ h}$ values were 462 and 713 h*ng/mL, the mean AUC_{last} values were 496 and 738 h*ng/mL, and the C_{max} values were 99.5 and 149 ng/mL. For 0.16 mg/kg and 0.32 mg/kg, respectively, the mean drug clearance (CL) was 331 and 484 mL/h/kg, and the mean apparent volume of distribution (Vz) were 3260 and 4640 mL/kg after the first infusion. At 0.16 mg/kg, the mean apparent terminal

elimination half-life (T½) was 6.74 hours, and at 0.32 mg/kg, it was 6.97 hours. Onfasprodil was not detected in samples taken prior to the infusion on Day 29, indicating the absence of onfasprodil accumulation after weekly or biweekly dosing.

Comparisons of mean concentrations at the end of infusion between Day 1 and Day 29 could not be executed appropriately because of the small number of samples on Day 29 (n=2 to 6 per treatment group) and the high variability of the concentrations. However, median concentrations at the end of infusion were comparable between Day 1 and Day 29, independent of the dosing regimen.

Supplementary Tables

Supplementary Table 1. ANCOVA analysis of change from baseline at 24 hours in the total MADRS score (ITT analysis set)

	Unadjusted arithmetic mean change from baseline (SD)		[n] Adjusted arithmetic mean change from baseline (SE)		Comparison of adjusted arithmetic mean difference: Test vs Ref.		
Treatment	**Test**	**Ref.**	**Test**	**Ref.**	**Diff**	**80% CI***	**P-value****
Pooled Onfasprodil 0.16 mg/kg (N=21) vs placebo (N=20)	-15.86 (8.2)	-7.40 (6.1)	[21] -15.51 (1.9)	[20] -7.27 (1.9)	-8.25	(-11.67, -4.83)	0.0013
Pooled Onfasprodil 0.32 mg/kg (N=19) vs placebo (N=20)	-12.79 (8.6)	-7.40 (6.1)	[19] -12.98 (1.9)	[20] -7.27 (1.9)	-5.71	(-9.22, -2.20)	0.0196
Ketamine (N=10) vs placebo (N=20)	-12.30 (12.3)	-7.40 (6.1)	[10] -12.94 (2.7)	[20] -7.27 (1.9)	-5.67	(-9.97, -1.38)	0.0461
Ketamine (N=10) vs pooled Onfasprodil 0.16 mg/kg (N=21)	-12.30 (12.3)	-15.86 (8.2)	[10] -12.94 (2.7)	[21] -15.51 (1.9)	2.57	(-1.73, 6.88)	0.7790
Ketamine (N=10) vs pooled Onfasprodil 0.32 mg/kg (N=19)	-12.30 (12.3)	-12.79 (8.6)	[10] -12.94 (2.7)	[19] -12.98 (1.9)	0.04	(-4.25, 4.33)	0.5043

The change from baseline in the total MADRS score at 24 hours after start of infusion was analyzed using an ANCOVA model. The model includes treatment as a group factor and baseline MADRS score as a covariate.
Baseline is defined to be the last available measurement obtained before the first infusion on Day 1.
*: two-sided CIs, **: one-sided p-value
N: The total number of subjects in the treatment group in this analysis.
n: The total number of subjects per treatment group and visit in this analysis.

Supplementary Table 2. ANCOVA analysis of change from baseline at 48 hours in the total MADRS score (ITT analysis set)

	Unadjusted arithmetic mean change from baseline (SD)		[n] Adjusted arithmetic mean change from baseline (SE)		Comparison of adjusted arithmetic mean difference: Test vs Ref.		
Treatment	**Test**	**Ref.**	**Test**	**Ref.**	**Diff**	**80% CI***	**P-value****
Pooled 0.16 mg/kg (N=19) vs placebo (N=19)	-15.00 (9.6)	-7.89 (8.9)	[19] -14.94 (2.2)	[19] -7.88 (2.2)	-7.06	(-11.06, -3.06)	0.0130
pooled 0.32 mg/kg (N=16) vs placebo (N=19)	-15.13 (8.9)	-7.89 (8.9)	[16] -15.25 (2.4)	[19] -7.88 (2.2)	-7.37	(-11.57, -3.18)	0.0133
Ketamine (N=4) vs placebo (N=19)	-19.00 (13.3)	-7.89 (8.9)	[4] -18.89 (4.8)	[19] -7.88 (2.2)	-11.02	(-17.80, -4.24)	0.0199
Ketamine (N=4) vs pooled 0.16 mg/kg (N=19)	-19.00 (13.3)	-15.00 (9.6)	[4] -18.89 (4.8)	[19] -14.94 (2.2)	-3.96	(-10.74, 2.82)	0.2259
Ketamine (N=4) vs pooled 0.32 mg/kg (N=16)	-19.00 (13.3)	-15.13 (8.9)	[4] -18.89 (4.8)	[16] -15.25 (2.4)	-3.64	(-10.55, 3.26)	0.2483

The change from baseline in the total MADRS score at 48 hours after start of infusion was analyzed using an ANCOVA model. The model includes treatment as a group factor and baseline MADRS score as a covariate.
Baseline is defined to be the last available measurement obtained before the first infusion on Day 1.
*: two-sided CIs, **: one-sided p-value
N: The total number of subjects in the treatment group in this analysis.
n: The total number of subjects per treatment group and visit in this analysis.

Supplementary Table 3. Secondary outcome measures (intent-to-treat analysis set)

	24 hours after the first infusion		48 hours after the first infusion		6 Weeks after the first infusion	
Treatment group	**Adjusted arithmetic mean change from baseline (SE)**	**Δ (90% CI)*; p-value****	**Adjusted arithmetic mean change from baseline (SE)**	**Δ (90% CI)*; p-value****	**Adjusted arithmetic mean change from baseline (SE)**	**Δ (90% CI)*; p-value****
MADRS suicidal thoughts						
Onfasprodil 0.16 mg/kg, weekly	−0.51 (0.2) n=11	−0.13 (−0.61, 0.35); 0.3325	−0.48 (0.2) n=9	−0.21 (−0.70, 0.29); 0.2491	−0.55 (0.3) n=8	−0.25 (−0.79, 0.29); 0.2201
Onfasprodil 0.16 mg/kg, biweekly	−0.83 (0.2) n=10	−0.45 (−0.95, 0.05); 0.0675	−0.83 (0.2) n=10	−0.55 (−1.05, −0.06); 0.0335	−0.41 (0.3) n=8	−0.12 (−0.66, 0.43); 0.3638
Onfasprodil 0.32 mg/kg, weekly	−0.69 (0.2) n=10	−0.31 (−0.81, 0.18); 0.1488	−0.80 (0.3) n=9	−0.52 (−1.03, −0.02); 0.0441	−0.31 (0.3) n=8	−0.01 (−0.56, 0.53); 0.4827
Onfasprodil 0.32 mg/kg, biweekly	−0.28 (0.3) n=9	0.10 (−0.41, 0.62); 0.6291	−0.20 (0.3) n=7	0.08 (−0.46, 0.62); 0.5911	−0.53 (0.3) n=6	−0.23 (−0.83, 0.37); 0.2632
Ketamine	−0.63 (0.2) n=10	−0.25 (−0.75, 0.25); 0.2029	−0.66 (0.3) n=4	−0.39 (−0.99, 0.22); 0.1461	−0.19 (0.3) n=9	0.10 (−0.42, 0.63); 0.6271
Placebo	−0.38 (0.2) n=20	-	−0.27 (0.2) n=19	-	−0.30 (0.2) n=17	-
Total BRMS score						
Onfasprodil 0.16 mg/kg, weekly	−11.66 (1.7) n=11	−5.70 (−9.28, −2.12); 0.0050	−10.00 (2.1) n=9	−3.35 (−7.63, 0.92); 0.0976	−7.21 (2.4) n=8	−1.13 (−6.08, 3.81); 0.3515
Onfasprodil 0.16 mg/kg, biweekly	−9.60 (1.8) n=10	−3.65 (−7.32, 0.03); 0.0512	−8.09 (2.1) n=10	−1.45 (−5.74, 2.85); 0.2877	−8.04 (2.6) n=8	−1.97 (−7.12, 3.18); 0.2627
Onfasprodil 0.32 mg/kg, weekly	−8.19 (1.8) n=10	−2.23 (−5.98, 1.51); 0.1615	−7.75 (2.2) n=9	−1.11 (−5.56, 3.34); 0.3389	−6.39 (2.6) n=8	−0.32 (−5.49, 4.85); 0.4591
Onfasprodil 0.32 mg/kg, biweekly	−7.10 (2.0) n=8	−1.14 (−5.03, 2.74); 0.3124	−6.97 (2.3) n=7	−0.33 (−4.94, 4.28); 0.4523	−6.39 (2.8) n=6	−0.32 (−5.76, 5.12); 0.4608
Ketamine	−7.24 (1.9) n=9	−1.28 (−5.03, 2.46); 0.2847	−7.11 (2.6) n=4	−0.47 (−5.46, 4.52); 0.4379	−8.34 (2.4) n=9	−2.27 (−7.24, 2.70); 0.2239
Placebo	−5.96 (1.3) n=20	-	−6.64 (1.5) n=19	-	−6.07 (1.7) N=17	-
Total CORE Melancholia score						
Onfasprodil 0.16 mg/kg, weekly	−4.76 (2.9) n=4	−1.14 (−7.05, 4.77); 0.3747	−5.77 (3.9) n=2	−0.71 (−7.94, 6.51); 0.4353	−5.79 (3.4) n=3	−0.59 (−7.17, 5.99); 0.4415
Onfasprodil 0.16 mg/kg, biweekly	−3.64 (3.6) n=3	−0.03 (−7.05, 7.00); 0.4975	−2.82 (3.7) n=3	2.24 (−4.86, 9.33); 0.6986	−4.82 (4.4) n=2	0.38 (−7.85, 8.61); 0.5305
Onfasprodil 0.32 mg/kg, weekly	−3.93 (3.0) n=4	−0.32 (−6.30, 5.67); 0.4653	−5.92 (3.2) n=3	−0.86 (−7.06, 5.34); 0.4097	−7.24 (3.5) n=3	−2.03 (−8.88, 4.81); 0.3118
Onfasprodil 0.32 mg/kg, biweekly	1.38 (3.5) n=3	4.99 (−1.56, 11.53); 0.8955	1.62 (4.0) n=2	6.68 (−0.51, 13.87); 0.9370	−6.49 (4.3) n=2	−1.28 (−9.13, 6.57); 0.3939

Ketamine	−5.07 (2.0) n=9	−1.46 (−6.11, 3.19); 0.3019	−6.68 (2.6) n=4	−1.62 (−6.94, 3.69); 0.3072	−9.01 (2.1) n=8	−3.80 (−8.64, 1.03); 0.0975
Placebo	−3.61 (2.0) n=8	-	−5.06 (1.9) n=9	-	−5.21 (2.1) n=8	-
Total KMDRS score						
Onfasprodil 0.16 mg/kg, weekly	−2.79 (0.9) n=11	−0.47 (−2.33, 1.40); 0.3400	−2.95 (1.0) n=9	−0.98 (−2.91, 0.95); 0.2022	−1.18 (1.0) n=8	0.41 (−1.65, 2.48); 0.6294
Onfasprodil 0.16 mg/kg, biweekly	−2.38 (0.9) n=10	−0.05 (−1.97, 1.86); 0.4815	−1.03 (0.9) n=10	0.94 (−0.98, 2.86); 0.7905	−1.06 (1.0) n=8	0.53 (−1.56, 2.63); 0.6622
Onfasprodil 0.32 mg/kg, weekly	−1.50 (1.0) n=10	0.82 (−1.13, 2.78); 0.7558	−1.97 (1.0) n=9	0.01 (−1.99, 2.00); 0.5022	−1.55 (1.1) n=8	0.04 (−2.09, 2.18); 0.5137
Onfasprodil 0.32 mg/kg, biweekly	−2.46 (1.0) n=9	−0.13 (−2.12, 1.85); 0.4557	−3.43 (1.1) n=7	−1.46 (−3.54, 0.63); 0.1246	−2.04 (1.2) n=6	−0.44 (−2.75, 1.86); 0.3754
Ketamine	−1.28 (1.0) N=10	1.04 (−0.88, 2.96); 0.8139	0.01 (1.3) n=4	1.99 (−0.39, 4.36); 0.9153	−1.68 (1.0) n=9	−0.09 (−2.11, 1.94); 0.4719
Placebo	−2.33 (0.7) n=20	-	−1.97 (0.7) n=19	-	−1.59 (0.7) n=17	-
	Day 22 (predose)		**Week 6**			
Total HAS	**LSM (SE)**	**Δ (90% CI)*; p-value****	**LSM (SE)**			**Δ (90% CI)*; p-value**
Onfasprodil 0.16 mg/kg, weekly	−3.42 (2.0) n=8	0.07 (−4.02, 4.16); 0.5111	−1.94 (2.0) n=8			2.85 (−1.23, 6.94); 0.8761
Onfasprodil 0.16 mg/kg, biweekly	−5.52 (2.0) n=8	−2.04 (−6.10, 2.03); 0.2035	−5.69 (2.0) n=8			−0.90 (−4.97, 3.17); 0.3572
Onfasprodil 0.32 mg/kg, weekly	−5.43 (1.9) n=9	−1.94 (−5.90, 2.01); 0.2074	−7.17 (2.0) n=8			−2.37 (−6.38, 1.65); 0.1644
Onfasprodil 0.32 mg/kg, biweekly	−2.75 (2.0) n=8	0.74 (−3.33, 4.81); 0.6190	−3.83 (2.2) n=6			0.97 (−3.30, 5.24); 0.6471
Ketamine	−1.99 (2.0) n=8	1.49 (−2.58, 5.57); 0.7283	−4.93 (2.0) n=8			−0.13 (−4.21, 3.94); 0.4786
Placebo	−3.49 (1.4) n=17	-	−4.80 (1.4) n=17			-

Δ, comparison of adjusted mean arithmetic treatment difference between onfasprodil and placebo**;** *, two-sided CIs; **, one-sided p-value; BRMS, Bech-Rafaelsen Melancholia Scale; CI, confidence interval; HAS, Hamilton Anxiety Scale; KMDRS, Koukopoulos Mixed Depression Rating Scale; LSM, least-square mean; MADRS, Montgomery-Åsberg Depression Rating Scale; SE, standard error

Supplementary Table 4. MMRM model of change from baseline at 24 hours, 48 hours, and Week 6 in the total MADRS score (ITT analysis set)

Analysis method: MMRM **Time point: 24h post 1st dose**	**Unadjusted arithmetic mean change from baseline (SD)**		**[n] Adjusted arithmetic mean change from baseline (SE)**		**Comparison of adjusted arithmetic mean difference: Test vs Ref.**		
Treatment	**Test**	**Ref.**	**Test**	**Ref.**	**Diff**	**80% CI***	**P-value****
Onfasprodil 0.16 mg/kg weekly (N=11) vs placebo (N=20)	-16.45 (8.2)	-7.40 (6.1)	[11] -15.78 (3.0)	[20] -7.23 (2.2)	-8.55	(-13.34, -3.77)	0.0112
Onfasprodil 0.32 mg/kg weekly (N=10) vs placebo (N=20)	-13.00 (8.0)	-7.40 (6.1)	[10] -13.69 (3.2)	[20] -7.23 (2.2)	-6.46	(-11.46, -1.46)	0.0490
Onfasprodil 0.16 mg/kg biweekly (N=10) vs placebo (N=20)	-15.20 (8.6)	-7.40 (6.1)	[10] -15.11 (3.1)	[20] -7.23 (2.2)	-7.89	(-12.79, -2.98)	0.0199
Onfasprodil 0.32 mg/kg biweekly (N=9) vs placebo (N=20)	-12.56 (9.7)	-7.40 (6.1)	[9] -12.13 (3.3)	[20] -7.23 (2.2)	-4.91	(-10.00, 0.18)	0.1082
Ketamine (N=10) vs placebo (N=20)	-12.30 (12.3)	-7.40 (6.1)	[10] -12.94 (3.2)	[20] -7.23 (2.2)	-5.71	(-10.70, -0.72)	0.0712
Onfasprodil 0.16 mg/kg weekly (N=11) vs Onfasprodil 0.32 mg/kg weekly (N=10)	-16.45 (8.2)	-13.00 (8.0)	[11] -15.78 (3.0)	[10] -13.69 (3.2)	-2.09	(-7.83, 3.64)	0.3197
Onfasprodil 0.16 mg/kg biweekly (N=10) vs Onfasprodil 0.32 mg/kg biweekly (N=9)	-15.20 (8.6)	-12.56 (9.7)	[10] -15.11 (3.1)	[9] -12.13 (3.3)	-2.98	(-8.81, 2.85)	0.2559
Onfasprodil 0.16 mg/kg weekly (N=11) vs Onfasprodil 0.16 mg/kg biweekly (N=10)	-16.45 (8.2)	-15.20 (8.6)	[11] -15.78 (3.0)	[10] -15.11 (3.1)	-0.67	(-6.24, 4.90)	0.4389
Onfasprodil 0.32 mg/kg weekly (N=10) vs Onfasprodil 0.32 mg/kg biweekly (N=9)	-13.00 (8.0)	-12.56 (9.7)	[10] -13.69 (3.2)	[9] -12.13 (3.3)	-1.55	(-7.50, 4.40)	0.3688

Analysis method: MMRM **Time point: 48 h post 1st dose**	**Unadjusted arithmetic mean change from baseline (SD)**		**[n] Adjusted arithmetic mean change from baseline (SE)**		**Comparison of adjusted arithmetic mean difference: Test vs Ref.**		
Treatment	**Test**	**Ref.**	**Test**	**Ref.**	**Diff**	**80% CI***	**P-value****
Onfasprodil 0.16 mg/kg weekly (N=11) vs placebo (N=20)	-15.78 (10.0)	-7.89 (8.9)	[9] -14.97 (3.1)	[19] -8.24 (2.2)	-6.73	(-11.61, -1.85)	0.0389
Onfasprodil 0.32 mg/kg weekly (N=10) vs placebo (N=20)	-14.89 (8.6)	-7.89 (8.9)	[9] -15.27 (3.2)	[19] -8.24 (2.2)	-7.03	(-12.11, -1.95)	0.0382
Onfasprodil 0.16 mg/kg biweekly (N=10) vs placebo (N=20)	-14.30 (9.8)	-7.89 (8.9)	[10] -14.21 (3.1)	[19] -8.24 (2.2)	-5.97	(-10.88, -1.05)	0.0600
Onfasprodil 0.32 mg/kg biweekly (N=9) vs placebo (N=20)	-15.43 (10.0)	-7.89 (8.9)	[7] -12.18 (3.4)	[19] -8.24 (2.2)	-3.94	(-9.19, 1.31)	0.1681
Ketamine (N=10) vs placebo (N=20)	-19.00 (13.3)	-7.89 (8.9)	[4] -11.75 (3.8)	[19] -8.24 (2.2)	-3.50	(-9.12, 2.12)	0.2119
Onfasprodil 0.16 mg/kg weekly (N=11) vs Onfasprodil 0.32 mg/kg weekly (N=10)	-15.78 (10.0)	-14.89 (8.6)	[9] -14.97 (3.1)	[9] -15.27 (3.2)	0.30	(-5.56, 6.16)	0.5263
Onfasprodil 0.16 mg/kg biweekly (N=10) vs Onfasprodil 0.32 mg/kg biweekly (N=9)	-14.30 (9.8)	-15.43 (10.0)	[10] -14.21 (3.1)	[7] -12.18 (3.4)	-2.03	(-7.99, 3.93)	0.3311
Onfasprodil 0.16 mg/kg weekly (N=11) vs Onfasprodil 0.16 mg/kg biweekly (N=10)	-15.78 (10.0)	-14.30 (9.8)	[9] -14.97 (3.1)	[10] -14.21 (3.1)	-0.76	(-6.40, 4.88)	0.4312
Onfasprodil 0.32 mg/kg weekly (N=10) vs Onfasprodil 0.32 mg/kg biweekly (N=9)	-14.89 (8.6)	-15.43 (10.0)	[9] -15.27 (3.2)	[7] -12.18 (3.4)	-3.09	(-9.26, 3.08)	0.2600

Analysis method: MMRM Time point: Week 6	Unadjusted arithmetic mean change from baseline (SD)		[n] Adjusted arithmetic mean change from baseline (SE)		Comparison of adjusted arithmetic mean difference: Test vs Ref.		
Treatment	**Test**	**Ref.**	**Test**	**Ref.**	**Diff**	**80% CI***	**P-value****
Onfasprodil 0.16 mg/kg weekly (N=11) vs placebo (N=20)	-14.38 (12.3)	-8.94 (10.6)	[8] -12.71 (3.4)	[17] -7.62 (2.3)	-5.09	(-10.37, 0.19)	0.1082
Onfasprodil 0.32 mg/kg weekly (N=10) vs placebo (N=20)	-13.13 (13.1)	-8.94 (10.6)	[8] -13.04 (3.5)	[17] -7.62 (2.3)	-5.42	(-10.83, -0.02)	0.0993
Onfasprodil 0.16 mg/kg biweekly (N=10) vs placebo (N=20)	-15.25 (12.2)	-8.94 (10.6)	[8] -14.08 (3.4)	[17] -7.62 (2.3)	-6.46	(-11.78, -1.15)	0.0598
Onfasprodil 0.32 mg/kg biweekly (N=9) vs placebo (N=20)	-10.67 (11.8)	-8.94 (10.6)	[6] -10.68 (3.9)	[17] -7.62 (2.3)	-3.06	(-8.86, 2.74)	0.2491
Ketamine (N=10) vs placebo (N=20)	-12.56 (13.9)	-8.94 (10.6)	[9] -12.86 (3.3)	[17] -7.62 (2.3)	-5.24	(-10.42, -0.06)	0.0974
Onfasprodil 0.16 mg/kg weekly (N=11) vs Onfasprodil 0.32 mg/kg weekly (N=10)	-14.38 (12.3)	-13.13 (13.1)	[8] -12.71 (3.4)	[8] -13.04 (3.5)	0.33	(-6.03, 6.69)	0.5266
Onfasprodil 0.16 mg/kg biweekly (N=10) vs Onfasprodil 0.32 mg/kg biweekly (N=9)	-15.25 (12.2)	-10.67 (11.8)	[8] -14.08 (3.4)	[6] -10.68 (3.9)	-3.40	(-10.02, 3.22)	0.2550
Onfasprodil 0.16 mg/kg weekly (N=11) vs Onfasprodil 0.16 mg/kg biweekly (N=10)	-14.38 (12.3)	-15.25 (12.2)	[8] -12.71 (3.4)	[8] -14.08 (3.4)	1.37	(-4.82, 7.56)	0.6118
Onfasprodil 0.32 mg/kg weekly (N=10) vs Onfasprodil 0.32 mg/kg biweekly (N=9)	-13.13 (13.1)	-10.67 (11.8)	[8] -13.04 (3.5)	[6] -10.68 (3.9)	-2.36	(-9.05, 4.33)	0.3254

The change from baseline in the total MADRS score was analyzed using MMRM reporting results for the post-baseline time points. The model includes the fixed, categorical effects of treatment, time and treatment × time interaction, as well as the continuous, fixed covariates of baseline score, and baseline score × time interaction. An AR(1) variance-covariance structure was used to model the within-subject errors.
Baseline is defined to be the last available measurement obtained before the first infusion on Day 1.
*: two-sided CIs, **: one-sided p-value
N: The total number of subjects in the treatment group in this analysis.
n: The total number of subjects per treatment group and visit in this analysis.

Supplementary Table 5. Change in CADSS and DES scores from baseline (safety analysis set)

Treatment group	24 hours		48 hours		6 Weeks	
	Adjusted arithmetic mean (SE)	**Δ (90% CI)*; p-value****	**Adjusted arithmetic mean (SE)**	**Δ (90% CI)*; p-value****	**Adjusted arithmetic mean (SE)**	**Δ (90% CI)*; p-value****
CADSS total score						
Onfasprodil 0.16 mg/kg, weekly	1.73 (0.7) n=11	1.73 (0.19, 3.26); 0.9680	0.20 (0.8) n=9	0.09 (−1.55, 1.74); 0.5371	0.90 (0.9) n=8	0.80 (−0.94, 2.54); 0.7748
Onfasprodil 0.16 mg/kg, biweekly	1.30 (0.8) n=10	1.30 (−0.28, 2.88) 0.9119	0.70 (0.8) n=10	0.60 (−1.00, 2.19); 0.7309	−0.02 (0.9) n=8	−0.13 (−1.87, 1.62); 0.4524
Onfasprodil 0.32 mg/kg, weekly	2.10 (0.8) n=10	2.10 (0.52, 3.68); 0.9854	4.41 (0.8) n=9	4.31 (2.66, 5.96); 1.000	0.19 (0.9) n=8	0.08 (−1.66, 1.83) 0.5313
Onfasprodil 0.32 mg/kg, biweekly	3.10 (0.9) n=8	3.10 (1.40, 4.81); 0.9986	3.37 (0.9) n=7	3.27 (1.47, 5.07); 0.9986	1.30 (1.0) n=6	1.20 (−0.73, 3.12); 0.8464
Ketamine	0.20 (0.8) n=10	0.20 (–1.38, 1.78); 0.5825	0.28 (1.2) n=4	0.18 (−2.03, 2.39); 0.5535	0.87 (0.8) n=9	0.76 (−0.92, 2.44); 0.7725
Placebo	−0.00 (0.6) n=20	-	0.10 (0.6) n=19	-	0.11 (0.6) n=17	-
DES total score						
Onfasprodil 0.16 mg/kg, weekly	1.82 (1.0) n=11	−0.68 (−2.79, 1.43); 0.2966	1.80 (1.1) n=9	−0.63 (−2.81, 1.55); 0.3164	1.38 (1.1) n=8	−1.24 (−3.49, 1.00); 0.1807
Onfasprodil 0.16 mg/kg, biweekly	2.00 (1.1) n=10	−0.50 (−2.67, 1.67); 0.3521	2.30 (1.1) n=10	−0.13 (−2.31, 2.05); 0.4604	1.61(1.1) n=8	−1.02 (−3.30, 1.26); 0.2303
Onfasprodil 0.32 mg/kg, weekly	1.20 (1.1) n=10	−1.30 (−3.47, 0.87); 0.1621	1.89 (1.1) n=9	−0.54 (−2.76, 1.68); 0.3435	1.02 (1.1) n=8	−1.60 (−3.88, 0.68); 0.1233
Onfasprodil 0.32 mg/kg, biweekly	7.22 (1.1) n=9	4.72 (2.47, 6.98); 0.9997	3.46 (1.2) n=7	1.02 (−1.33, 3.38); 0.7634	0.24 (1.3) n=6	−2.39 (−4.83, 0.06); 0.0541
Ketamine	2.10 (1.1) n=10	−0.40 (−2.57, 1.77); 0.3806	1.89 (1.4) n=4	−0.54 (−3.15, 2.06); 0.3651	1.86 (1.1) n=9	−0.76 (−3.00, 1.48); 0.2872
Placebo	2.50 (0.8) n=20	-	2.43 (0.8) n=19	-	2.63 (0.8) n=17	-

The total CADSS and DES score at 24 hours, 48 hours, and 6 weeks after start of infusion is presented.**Δ,** comparison of adjusted mean arithmetic treatment difference between onfasprodil and placebo**;** *, two-sided CIs; **, one-sided p-value; CADSS, Clinician-Administered Dissociative States Scale; CI, confidence interval; DES, Dissociative Experiences Scale; LSM, least square mean; SE, standard error

Supplementary Table 6. Overall incidence of AEs

	Onfasprodil 0.16 mg/kg weekly N=11	**Onfasprodil 0.16 mg/kg biweekly N=10**	**Onfasprodil 0.32 mg/kg weekly N=10**	**Onfasprodil 0.32 mg/kg biweekly N=9**	**Ketamine N=10**	**Placebo N=20**	**Total N=70**
	nE, nS (%)	**nE, nS (%)**	**nE, nS (%)**	**nE, nS (%)**	**nE, nS (%)**	**nE, nS (%)**	**nE, nS (%)**
AEs, patients with AEs	43, 7 (63.6)	17, 6 (60.0)	52, 7 (70.0)	28, 6 (66.7)	69, 6 (60.0)	14, 7 (35.0)	223, 39 (55.7)
Mild	29, 5 (45.5)	15, 6 (60.0)	39, 7 (70.0)	14, 3 (33.3)	69, 6 (60.0)	9, 5 (25.0)	175, 32 (45.7)
Moderate	11, 3 (27.3)	1, 1 (10.0)	11, 3 (30.0)	9, 5 (55.6)	0	2, 1 (5.0)	34, 13 (18.6)
Severe	3, 2 (18.2)	1, 1 (10.0)	2, 1 (10.0)	4, 3 (33.3)	0	3, 3 (15.0)	13, 10 (14.3)
Life-threatening	0	0	0	1, 1 (11.1)	0	0	1, 1 (1.4)
Study drug-related AEs	35, 5 (45.5)	13, 5 (50.0)	46, 7 (70.0)	21, 5 (55.6)	65, 6 (60.0)	12, 5 (25.0)	192, 33 (47.1)
SAEs	0	1, 1 (10.0)	0	3, 3 (33.3)	0	1, 1 (5.0)	5, 5 (7.1)
AEs leading to discontinuation of study treatment	4, 1 (9.1)	0	0	2, 2 (22.2)	0	1, 1 (5.0)	7, 4 (5.7)
Study drug-related AEs leading to discontinuation of study treatment	0	0	0	0	0	1, 1 (5.0)	1, 1 (1.4)

AE, adverse event; SAE, serious AE; N, number of patients studied; nE, number of AE events in the category; nS, number of patients with at least one AE in the category. % is based on the number of patients. A single occurrence was counted if there was ≤1 day gap between the end date of the preceding AE and the start date of the consecutive AE.

Supplementary Table 7. Incidence of AEs by primary system organ class (safety analysis set)

	Onfasprodil 0.16 mg/kg weekly N=11	Onfasprodil 0.16 mg/kg biweekly N=10	Onfasprodil 0.32 mg/kg weekly N=10	Onfasprodil 0.32 mg/kg biweekly N=9	Pooled Onfasprodil 0.16 mg/kg N=21	Pooled Onfasprodil 0.32 mg/kg N=19	Ketamine N=10	Placebo N=20	Total N=70
Primary system organ class	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with at least 1 AE	7 (63.6)	6 (60.0)	7 (70.0)	6 (66.7)	13 (61.9)	13 (68.4)	6 (60.0)	7 (35.0)	39 (55.7)
System organ class									
Nervous system disorders	4 (36.4)	5 (50.0)	7 (70.0)	4 (44.4)	9 (42.9)	11 (57.9)	5 (50.0)	3 (15.0)	28 (40.0)
Psychiatric disorders	4 (36.4)	2 (20.0)	4 (40.0)	4 (44.4)	6 (28.6)	8 (42.1)	5 (50.0)	4 (20.0)	23 (32.9)
General disorders and administration site conditions	3 (27.3)	1 (10.0)	3 (30.0)	1 (11.1)	4 (19.0)	4 (21.1)	3 (30.0)	2 (10.0)	13 (18.6)
Gastrointestinal disorders	0	3 (30.0)	1 (10.0)	1 (11.1)	3 (14.3)	2 (10.5)	4 (40.0)	1 (5.0)	10 (14.3)
Investigations	3 (27.3)	1 (10.0)	0	0	4 (19.0)	0	1 (10.0)	0	5 (7.1)
Infections and infestations	1 (9.1)	0	3 (30.0)	0	1 (4.8)	3 (15.8)	0	0	4 (5.7)
Eye disorders	1 (9.1)	0	0	0	1 (4.8)	0	2 (20.0)	0	3 (4.3)
Skin and subcutaneous tissue disorders	0	0	1 (10.0)	0	0	1 (5.3)	2 (20.0)	0	3 (4.3)
Ear and labyrinth disorders	0	0	0	0	0	0	2 (20.0)	0	2 (2.9)
Injury, poisoning and procedural complications	0	0	0	1 (11.1)	0	1 (5.3)	0	1 (5.0)	2 (2.9)
Cardiac disorders	0	0	0	1 (11.1)	0	1 (5.3)	0	0	1 (1.4)
Metabolism and nutrition disorders	0	1 (10.0)	0	0	1 (4.8)	0	0	0	1 (1.4)
Musculoskeletal and connective tissue disorders	1 (9.1)	0	0	0	1 (4.8)	0	0	0	1 (1.4)
Respiratory, thoracic and mediastinal disorders	0	1 (10.0)	0	0	1 (4.8)	0	0	0	1 (1.4)

Arranged in descending order of frequency (in total group) and alphabetically by SOC.

Supplementary Table 8. Incidence of AEs (occurring in at least 3 subjects) by preferred term (safety analysis set)

	Onfasprodil 0.16 mg/kg weekly N=11	Onfasprodil 0.16 mg/kg biweekly N=10	Onfasprodil 0.32 mg/kg weekly N=10	Onfasprodil 0.32 mg/kg biweekly N=9	Pooled Onfasprodil 0.16 mg/kg N=21	Pooled Onfasprodil 0.32 mg/kg N=19	Ketamine N=10	Placebo N=20	Total N=70
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Subjects with at least 1 AE	7 (63.6)	6 (60.0)	7 (70.0)	6 (66.7)	13 (61.9)	13 (68.4)	6 (60.0)	7 (35.0)	39 (55.7)
Preferred term									
Amnesia	2 (18.2)	0	5 (50.0)	3 (33.3)	2 (9.5)	8 (42.1)	0	0	10 (14.3)
Dizziness	2 (18.2)	3 (30.0)	1 (10.0)	1 (11.1)	5 (23.8)	2 (10.5)	2 (20.0)	1 (5.0)	10 (14.3)
Somnolence	2 (18.2)	1 (10.0)	4 (40.0)	0	3 (14.3)	4 (21.1)	1 (10.0)	0	8 (11.4)
Feeling abnormal	3 (27.3)	1 (10.0)	2 (20.0)	0	4 (19.0)	2 (10.5)	0	0	6 (8.6)
Headache	1 (9.1)	0	2 (20.0)	1 (11.1)	1 (4.8)	3 (15.8)	1 (10.0)	1 (5.0)	6 (8.6)
Depersonalisation/derealisation disorder	0	0	0	0	0	0	5 (50.0)	0	5 (7.1)
Fatigue	0	0	2 (20.0)	1 (11.1)	0	3 (15.8)	1 (10.0)	1 (5.0)	5 (7.1)
Dry mouth	0	0	0	0	0	0	3 (30.0)	1 (5.0)	4 (5.7)
Nausea	0	1 (10.0)	1 (10.0)	0	1 (4.8)	1 (5.3)	2 (20.0)	0	4 (5.7)
Ataxia	0	0	1 (10.0)	2 (22.2)	0	3 (15.8)	0	0	3 (4.3)
Blood pressure increased	2 (18.2)	1 (10.0)	0	0	3 (14.3)	0	0	0	3 (4.3)
Confusional state	0	0	1 (10.0)	1 (11.1)	0	2 (10.5)	0	1 (5.0)	3 (4.3)
Dissociation	2 (18.2)	0	0	0	2 (9.5)	0	0	1 (5.0)	3 (4.3)
Insomnia	2 (18.2)	0	0	0	2 (9.5)	0	0	1 (5.0)	3 (4.3)
Memory impairment	2 (18.2)	0	1 (10.0)	0	2 (9.5)	1 (5.3)	0	0	3 (4.3)
Paraesthesia	1 (9.1)	0	0	0	1 (4.8)	0	1 (10.0)	1 (5.0)	3 (4.3)

Preferred terms are sorted in descending frequency, as reported in the "Total" column.

Supplementary Table 9. Incidence of AEs of interest (safety analysis set)

	Onfasprodil 0.16 mg/kg weekly	Onfasprodil 0.16 mg/kg biweekly	Onfasprodil 0.32 mg/kg weekly	Onfasprodil 0.32 mg/kg biweekly	Pooled Onfasprodil 0.16 mg/kg	Pooled Onfasprodil 0.32 mg/kg	Ketamine	Placebo	Total
	N=11	N=10	N=10	N=9	N=21	N=19	N=10	N=20	N=70
AE of interest	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Amnesia	2 (18.2)	0	5 (50.0)	3 (33.3)	2 (9.5)	8 (42.1)	0	0	10 (14.3)
Dissociation	4 (36.4)	1 (10.0)	3 (30.0)	2 (22.2)	5 (23.8)	5 (26.3)	5 (50.0)	2 (10.0)	17 (24.3)
Sedation	2 (18.2)	1 (10.0)	4 (40.0)	0	3 (14.3)	4 (21.1)	1 (10.0)	0	8 (11.4)
Dissociation and amnesia	2 (18.2)	0	1 (10.0)	0	2 (9.5)	1 (5.3)	0	0	3 (4.3)
Vomiting	0	0	1 (10.0)	0	0	1 (5.3)	0	0	1 (1.4)

Supplementary Table 10. Time (hours) to onset of treatment-related AEs of interest (safety analysis set)

AE of interest	Onfasprodil 0.16 mg/kg weekly N=4	Onfasprodil 0.16 mg/kg biweekly N=2	Onfasprodil 0.32 mg/kg weekly N=7	Onfasprodil 0.32 mg/kg biweekly N=5	Pooled Onfasprodil 0.16 mg/kg N=6	Pooled Onfasprodil 0.32 mg/kg N=12	Ketamine N=4	Placebo N=2	Total N=24
Amnesia									
Mean (SD) [n]	0.45 (0.141) [2]	--	0.40 (0.263) [5]	0.36 (0.268) [3]	0.45 (0.141) [2]	0.38 (0.246) [8]	--	--	0.40 (0.224) [10]
Median [Min – Max]	0.45 [0.4, 0.6]	--	0.40 [0.0, 0.7]	0.25 [0.2, 0.7]	0.45 [0.4, 0.6]	0.37 [0.0, 0.7]	--	--	0.38 [0.0, 0.7]
Dissociation									
Mean (SD) [n]	0.52 (0.131) [4]	0.33 [1]	0.30 (0.233) [3]	0.62 (0.059) [2]	0.49 (0.142) [5]	0.43 (0.244) [5]	0.10 (0.041) [4]	0.51 (0.719) [2]	0.37 (0.290) [16]
Median [Min – Max]	0.54 [0.4, 0.7]	0.33 [0.3, 0.3]	0.40 [0.0, 0.5]	0.62 [0.6, 0.7]	0.53 [0.3, 0.7]	0.47 [0.0, 0.7]	0.09 [0.1, 0.2]	0.51 [0.0, 1.0]	0.38 [0.0, 1.0]
Dissociation and Amnesia									
Mean (SD) [n]	0.45 (0.141) [2]	--	0.40 [1]	--	0.45 (0.141) [2]	0.40 [1]	--	--	0.43 (0.104) [3]
Median [Min – Max]	0.45 [0.4, 0.6]	--	0.40 [0.4, 0.4]	--	0.45 [0.4, 0.6]	0.40 [0.4, 0.4]	--	--	0.40 [0.4, 0.6]
Sedation									
Mean (SD) [n]	0.33 (0.177) [2]	0.10 [1]	1.46 (1.983) [4]	--	0.25 (0.180) [3]	1.46 (1.983) [4]	0.10 [1]	--	0.84 (1.464) [8]
Median [Min – Max]	0.33 [0.2, 0.5]	0.10 [0.1, 0.1]	0.63 [0.2, 4.4]	--	0.20 [0.1, 0.5]	0.63 [0.2, 4.4]	0.10 [0.1, 0.1]	--	0.23 [0.1, 4.4]

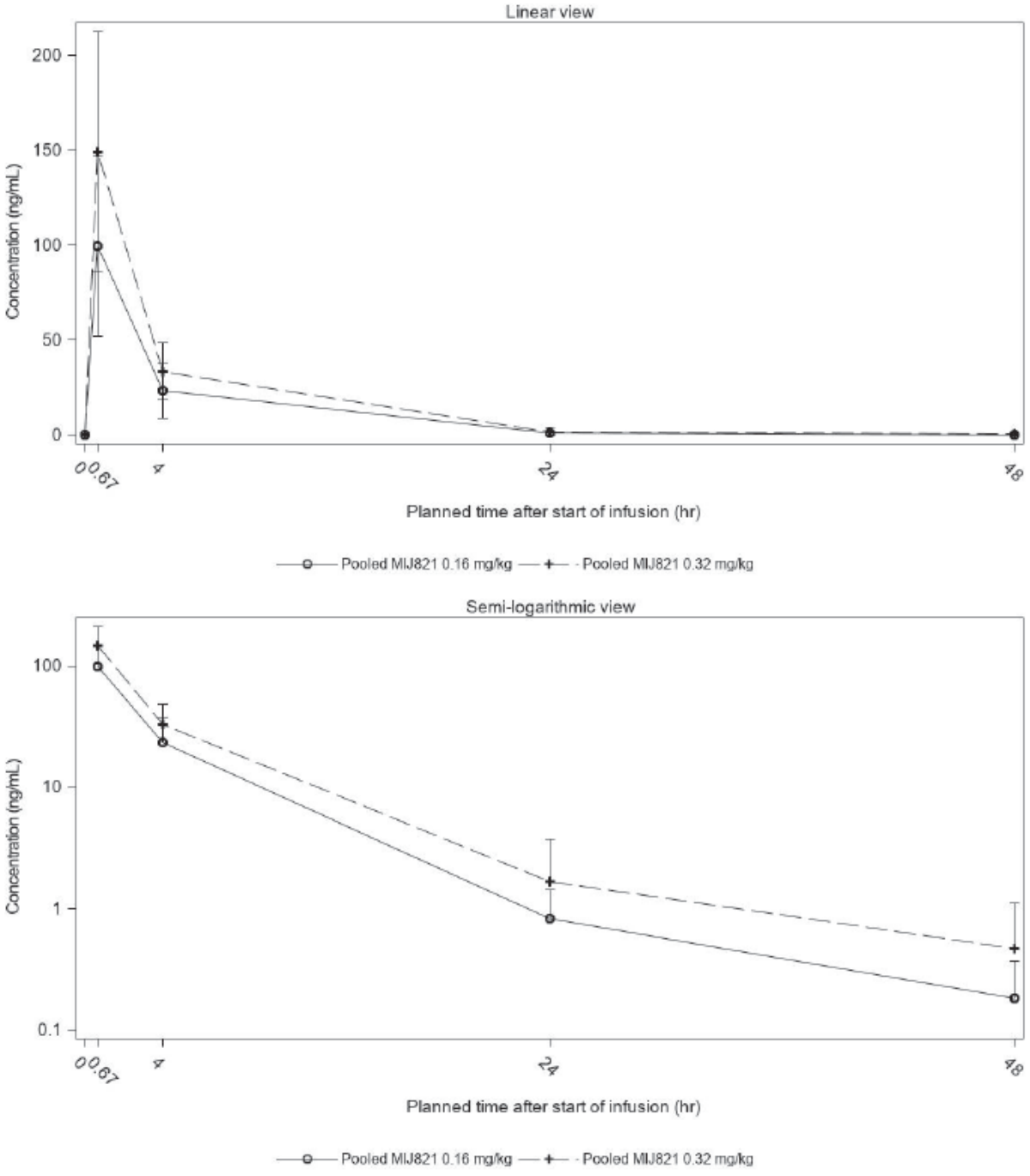
n –number of subjects with a given AE.
Time to onset refers to the time between the date/time of the most recent dose and the start date/time of AE.
If a subject had multiple events in an AE of interest, only the minimum onset time was considered.

Supplementary Table 11. Resolution time (hours) of treatment-related AEs of interest (safety analysis set)

AE of interest	Onfasprodil 0.16 mg/kg weekly N=4	Onfasprodil 0.16 mg/kg biweekly N=2	Onfasprodil 0.32 mg/kg weekly N=7	Onfasprodil 0.32 mg/kg biweekly N=5	Pooled Onfasprodil 0.16 mg/kg N=6	Pooled Onfasprodil 0.32 mg/kg N=12	Ketamine N=4	Placebo N=2	Total N=24
Amnesia									
Mean (SD) [n]	5.13 (2.652) [2]	--	2.97 (3.627) [5]	3.39 (2.084) [3]	5.13 (2.652) [2]	3.13 (2.967) [8]	--	--	3.53 (2.887) [10]
Median [Min – Max]	5.13 [3.3, 7.0]	--	1.00 [0.7, 9.2]	4.33 [1.0, 4.8]	5.13 [3.3, 7.0]	2.14 [0.7, 9.2]	--	--	3.27 [0.7, 9.2]
Dissociation									
Mean (SD) [n]	4.01 (2.591) [4]	5.25 [1]	2.86 (0.933) [3]	4.14 (0.200) [2]	4.26 (2.311) [5]	3.37 (0.968) [5]	1.27 (0.704) [4]	1.99 (0.012) [2]	2.95 (1.810) [16]
Median [Min – Max]	3.75 [1.6, 7.0]	5.25 [5.3, 5.3]	3.00 [1.9, 3.7]	4.14 [4.0, 4.3]	5.25 [1.6, 7.0]	3.72 [1.9, 4.3]	1.02 [0.8, 2.3]	1.99 [2.0, 2.0]	2.23 [0.8, 7.0]
Dissociation and Amnesia									
Mean (SD) [n]	6.17 (1.179) [2]	--	3.72 [1]	--	6.17 (1.179) [2]	3.72 [1]	--	--	5.35 (1.642) [3]
Median [Min – Max]	6.17 [5.3, 7.0]	--	3.72 [3.7, 3.7]	--	6.17 [5.3, 7.0]	3.72 [3.7, 3.7]	--	--	5.33 [3.7, 7.0]
Sedation									
Mean (SD) [n]	0.97 (0.896) [2]	4.00 [1]	2.72 (0.994) [4]	--	1.98 (1.862) [3]	2.72 (0.994) [4]	0.47 [1]	--	2.16 (1.420) [8]
Median [Min – Max]	0.97 [0.3, 1.6]	4.00 [4.0, 4.0]	2.50 [1.9, 4.0]	--	1.60 [0.3, 4.0]	2.50 [1.9, 4.0]	0.47 [0.5, 0.5]	--	1.93 [0.3, 4.0]

n – number of subjects with a given AE.
Resolution time refers to the time between the start date/time and the end date/time of AE.
If a subject had multiple events in an AE of interest, only the maximum of the AE duration was considered.

Supplementary Figure 1. Mean plasma concentration time-plot per treatment (overlaying) (PK analysis set)



Data presented are mean (SD). PK, pharmacokinetics; SD, standard deviation

Note: Onfasprodil is also referred as MIJ821