The Journal of Clinical Psychiatry

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

Authors: Richard C. Shelton, MD; Robert E. Litman, MD; Howard Hassman, DO; David P. Walling, PhD; Salvador Ros Montalbán, MD; Joan Salvà Coll, MD; John Zajecka, MD; Oleksandr Sverdlov, PhD; Baltazar Gomez-Mancilla, MD, PhD; Mark P. Healy, PhD; Y. Gopi Shanker, PhD; Maria Berkheimer, PhD; Thomas Faller, PhD; Florian von Raison, MD; Carmen Serban, MD; Jang-Ho Cha, MD, PhD; and S. Nassir Ghaemi, MD, MPH

DOI Number: 10.4088/JCP.23m15246

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

© Physicians Postgraduate Press, Inc.

The Journal of Clinical Psychiatry

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

DISCLAIMER

This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

© Physicians Postgraduate Press, Inc.

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).

References

1. Muller MJ, Himmerich H, Kienzle B, Szegedi A. Differentiating moderate and severe depression using the Montgomery-Asberg depression rating scale (MADRS). J Affect Disord. 2003;77(3):255-60.
2. Bremner JD, Krystal JH, Putnam FW, et al. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). J Trauma Stress. Jan 1998;11(1):125-36.
3. Guy W. Clinical Global Impression. ECDEU Assessment Manual for Psychopharmacology, revised National Institute of Mental Health, Rockville, MD. 1976.
4. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry. 1978;133:429-35.
5. Bech P, Gram LF, Dein E, et al. Quantitative rating of depressive states. Acta Psychiatr Scand. 1975;51:161-70.
6. Parker G, McCraw S. 2017. The properties and utility of the CORE measure of melancholia. J of Affective Disorders. 2017;207:128-135.
7. Sani G, Vöhringer PA, Barroilhet SA, et al (2018) The Koukopoulos Mixed Depression Rating Scale (KMDRS): An International Mood Network (IMN) validation study of a new mixed mood rating scale. J Affect Disord. 2018;232:9-16.
8. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol. 1959;32:50-5.

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]

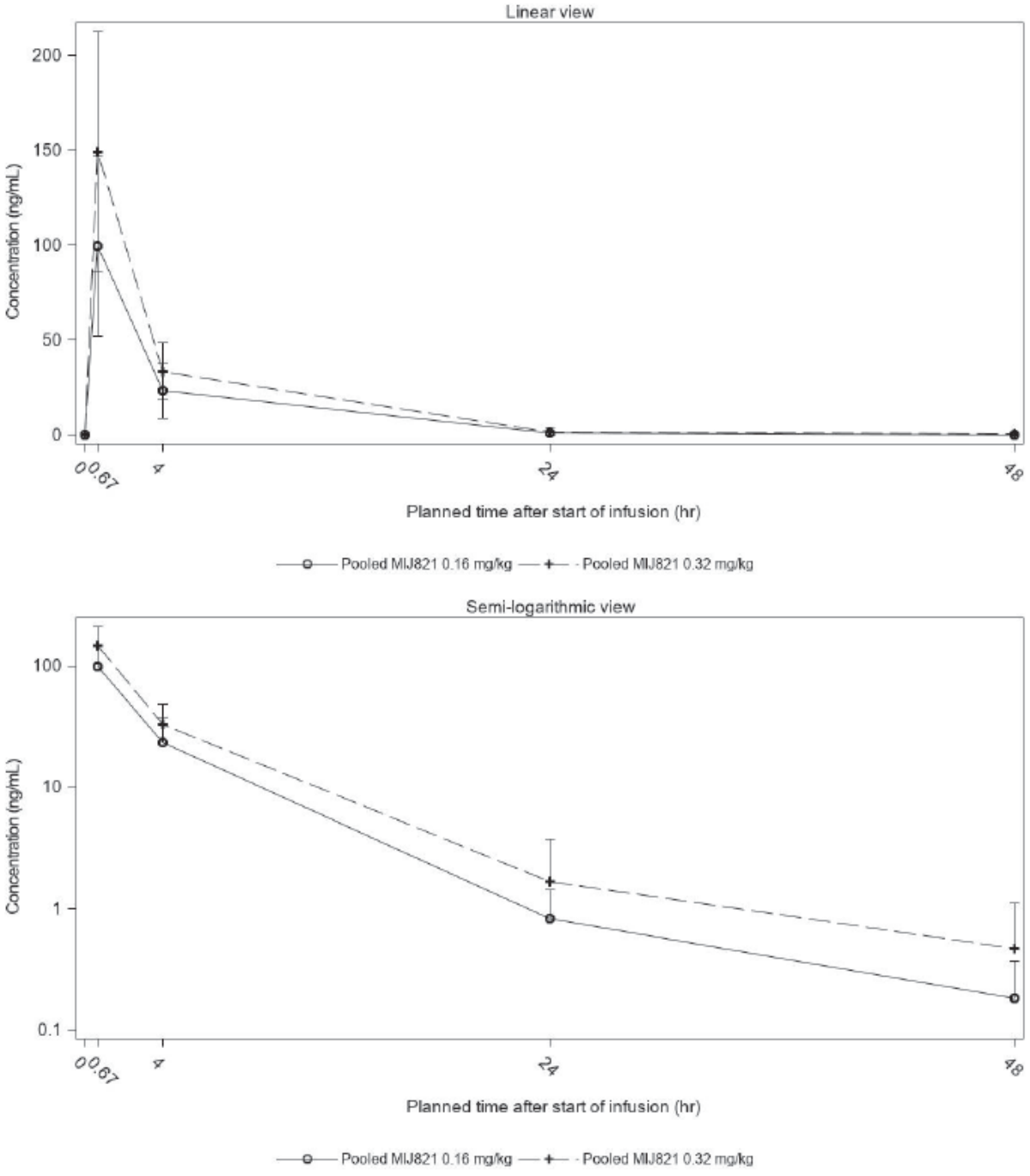
n –number of subjects with a given AE.
Time to onset refers to the time between the date/time of the most recent dose and the start date/time of AE.
If a subject had multiple events in an AE of interest, only the minimum onset time was considered.

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