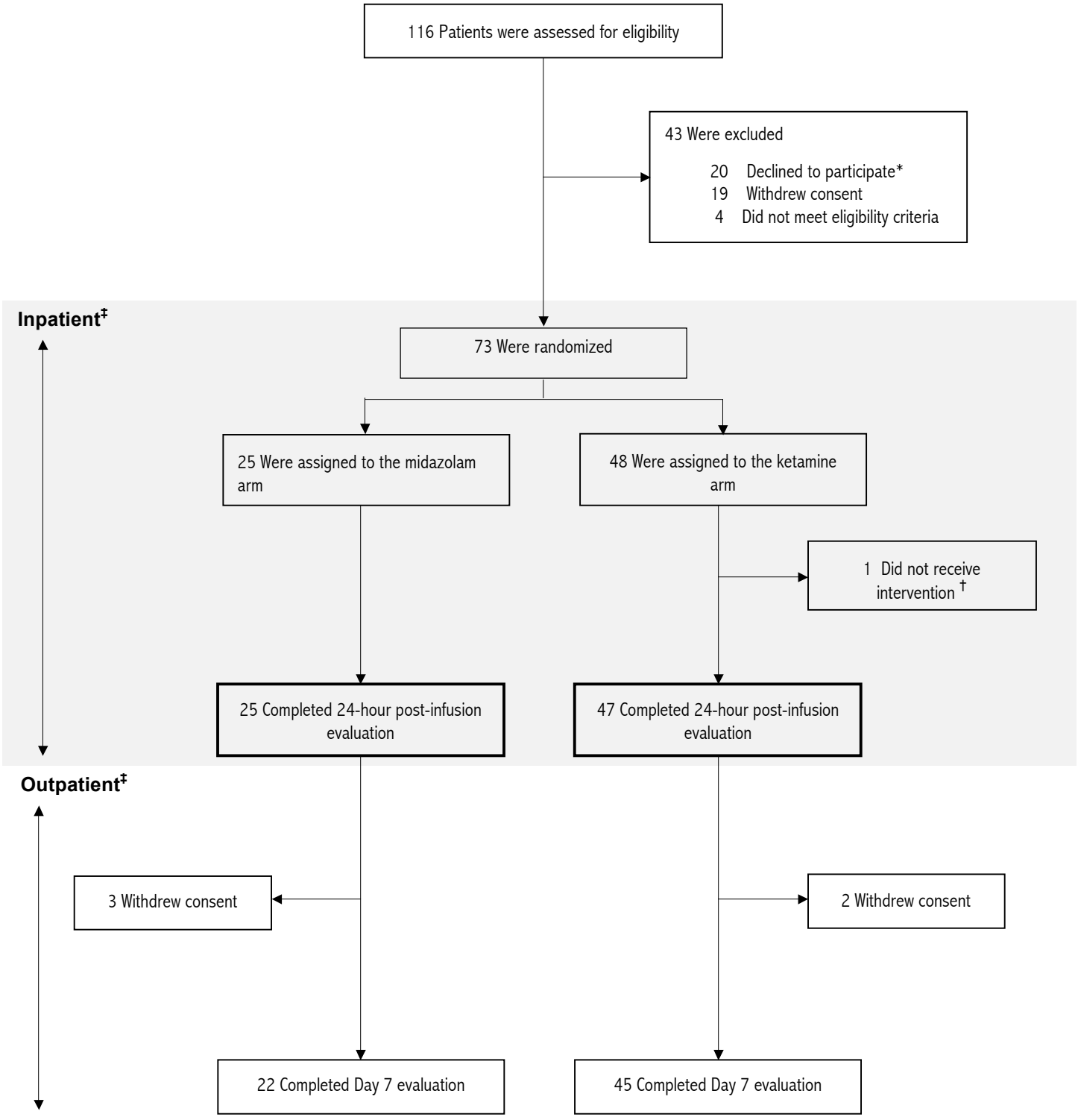
Supplementary Material for:

Antidepressant Efficacy of Ketamine in Treatment-Resistant Major Depression: A Two-Site, Randomized Controlled Trial

I. Figures

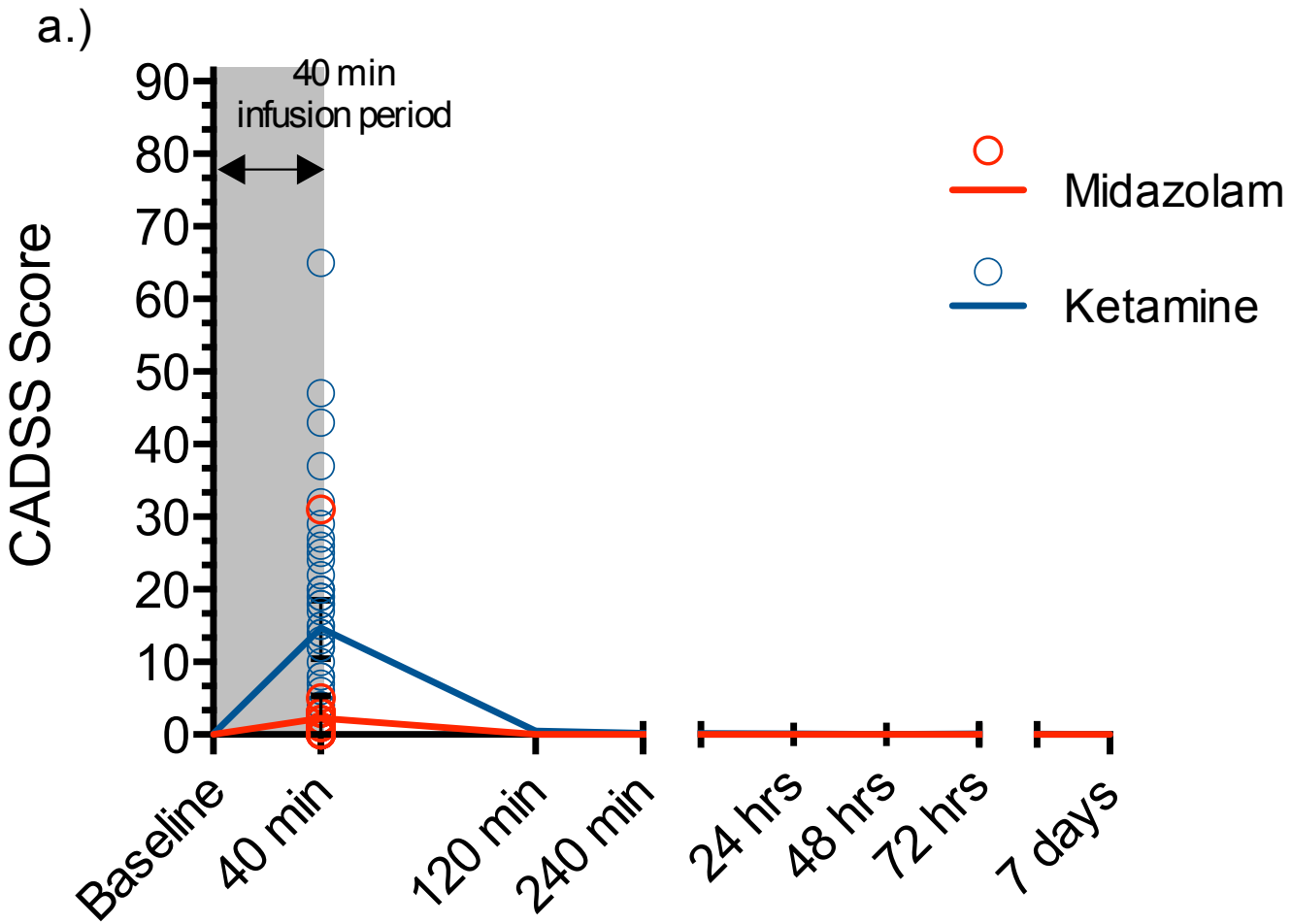
I.a. SF1. CONSORT diagram



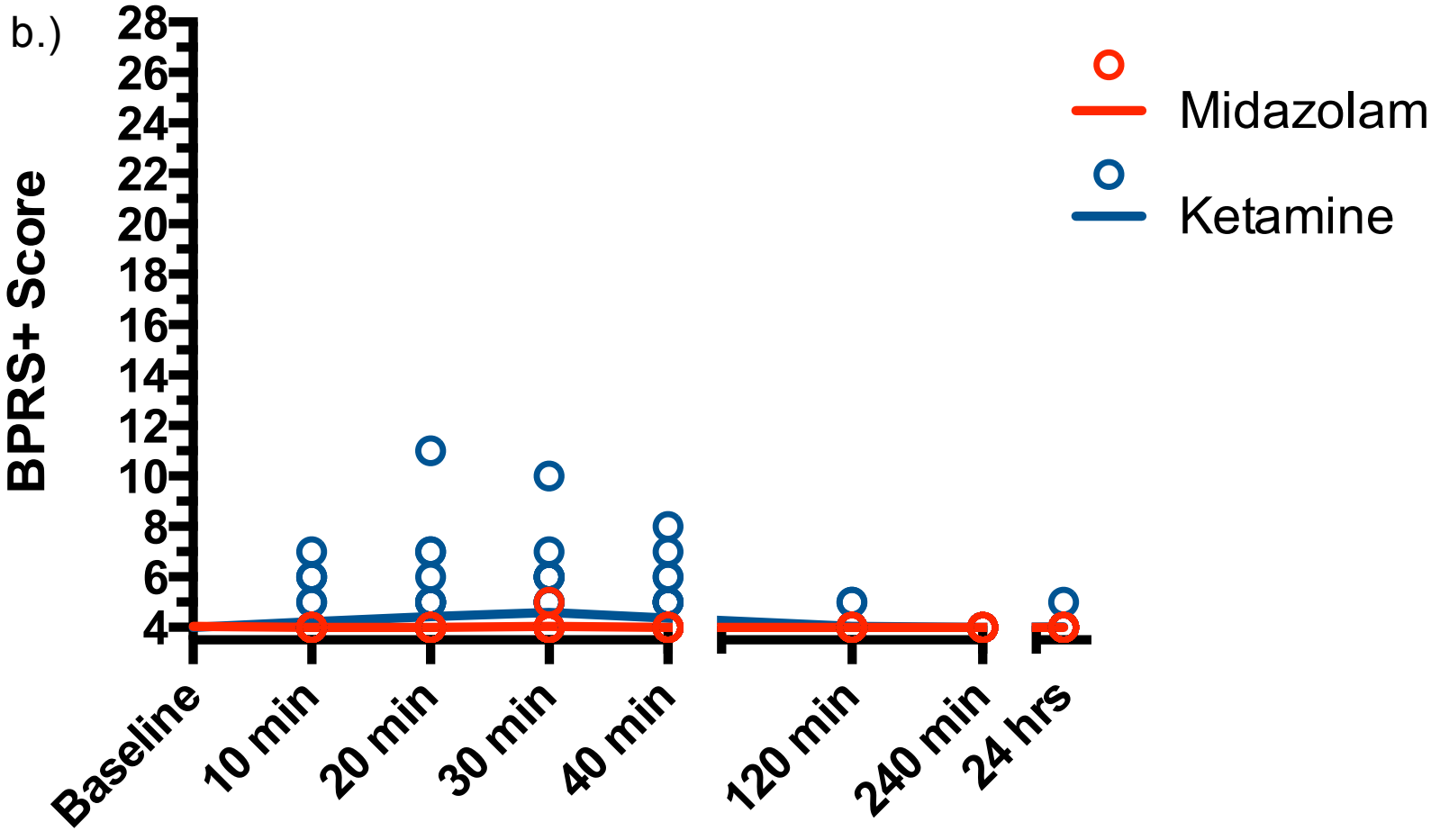
*Patients declined to participate due to taper/washout-out concerns. † Patient did not receive intervention due to elevated blood pressure. ‡ Patients were admitted into the hospital the day before infusion. Assessments at 40 min, 120 min, 240 min, 8 hours, and 24 hours post-infusion were conducted during the inpatient period. Assessments at 48 hours, 72 hours, and 7 days post-infusion were conducted on an outpatient basis.

I.b.

SF2. Psychoactive Side Effects of Study Drug



SF2.a.) Clinician Administered Dissociative States Scale (CADSS) scores for patients randomized to Ketamine (blue) and Midazolam (red) groups at baseline, 40 min, 120 min, 240 min, 24 hrs, 48 hrs, 72 hrs, and 7 days post-infusion. At 40 min, the average score for the Ketamine group was 14.7 (10.6-18.8, 95% CI), and 2.28 (0.0-4.8, 95% CI) for the Midazolam group. Average CADSS scores for the Ketamine group beyond the 40 min time point ranged between 0.065 and 0.533



SF2 b.) Brief Psychiatric Rating Scale positive symptom subscale (BPRS+) scores for patients randomized to Ketamine (blue) and Midazolam (red) groups at baseline, 10, 20, 30, 40, 120, 240 min, and 24 hours post-infusion. Average BPRS+ scores for Ketamine patients beyond the 40min time point ranged from 4.02 to 4.04.

II. Tables

II. a. ST1. Efficacy Outcomes at Seven Days Post-Infusion

Variable	Ketamine	Midazolam	Test Statistic
	Mean (95% C.I.)[a]	*Mean (95% C.I.)*[b]	
Montgomery-Asberg Depression Rating Scale (MADRS)	17.85 (14.29-21.42)	23.54 (18.29-28.79)	t(64) = 1.88, $P \leq 0.065$
Quick Inventory of Depressive Symptomatology-Self Report	8.58 (6.92-10.24)	11.42 (8.87-13.97)	t(61) = 1.90, $P \leq 0.062$
	Proportion	*Proportion*	
Response	45.7% (*n*=21)	18.2% (*n*=4)	Exact $P \leq 0.051$
Clinical Global Impression Scale-Improvement	46.7% (*n*=21)	20.0% (*n*=4)	Exact $P \leq 0.064$
Clinical Global Impression Scale-Severity	44.4% (*n*=20)	15.0% (*n*=3)	Exact $P \leq 0.028$

[a] Least square means adjusting for site and baseline value.

[b] Response defined as greater than or equal to 50% reduction in MADRS score from baseline.

II. b. ST2. Psychoactive Side Effect Ratings at 40 minutes Post-Infusion

	40 Minute Post-Infusion Ratings					
Scale	**Ketamine (*n*=47)**			**Midazolam (*n*=25)**		
	mean (SD)	*range (min-max)*	*95% CI*	*mean (SD)*	*range (min-max)*	*95% CI*
Brief Psychiatric Rating Scale^{+} (BPRS^{+})[a]	4.4 (0.8)	4-8	4.1-4.61	4.0 (0)	4	4.0-4.0
Clinician-Administered Dissociative States Scale (CADSS)[b]	14.7 (14.0)	0-65	10.6-18.8	2.3 (6.1)	0-31	0.0-4.8
Young Mania Rating Scale (YMRS, Item 1)[c]	0.6 (1.0)	0-3	0.0-0.9	0.12 (0.3)	0-1	0.0-0.26

[a] The BPRS^{+} is an abridged version of the BPRS incorporating four key BPRS items for the positive symptoms of psychosis: conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content. Scores range from 4 to 28.

[b] Scores on the CADSS range from 0 to 92, with 23 items rated on a scale from 0 to 4.

[c] The first item of the YMRS is rated on a scale of 0 (absent elevation in mood) to 4 (euphoric).

II. c. ST3. List of Serious Adverse Events (SAEs)

Patient ID	Week/Phase in Study	Expected?	Relation to Study Drug	Description of SAE	Intervention/Outcome
Patient 1	Day of Infusion	No	Possible	Hypotension (BP=73/40 for 1 min)/bradycardia (HR <30 bpm for 30 sec, followed by spontaneous recovery). This occurred while the subject was undergoing venipuncture at the 30 min time point and was considered a vaso- vagal episode.	Ketamine infusion was terminated. IV ephedrine and atropine were administered, which stabilized the patient's heart rate and blood pressure. The patient was continued on cardiac monitoring with telemetry for 24 hours and then discharged home in stable condition.
Patient 2	Taper/Wash-Out Phase	Yes	None	Suicide Attempt: While tapering off of psychotropic medication, patient was hospitalized following an attempted overdose.	Patient required admission to the intensive care unit, and was then transferred to an inpatient psychiatric unit. Patient was discharged in stable condition.