A RANDOMIZED, PLACEBO-CONTROLLED, EXPLORATORY, DOUBLE-BLIND STUDY TO ASSESS THE SAFETY AND EFFICACY OF INTRAVENOUS PCN-101 IN TREATMENT RESISTANT DEPRESSION

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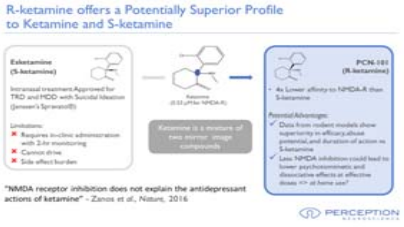
Introduction

Perception Neuroscience, is developing the R-isomer of ketamine (PCN-101, R-ketamine, arketamine) for the treatment of Treatment Resistant Depression (TRD).

Chemically, ketamine is a mixture of two enantiomers, the R- and the S-forms. S-ketamine (esketamine, Spravato©) has been developed and marketed by Janssen for TRD. S-ketamine has approximately 4-fold higher affinity for the NMDA-receptor, which is thought to drive the dissociative side effects of ketamine. However, data from preclinical models indicate that NMDA antagonism alone does not explain the antidepressant actions of ketamine.

Evidence from nonclinical depression model studies of subanesthetic doses in rodents, and both nonclinical and preliminary clinical studies suggest that R-ketamine may have a more favorable safety profile with a decreased incidence of adverse events (AEs) (eg, dissociative, cognitive impairment, and psychotomimetic effects) compared with S-ketamine.

Based on nonclinical studies, R-ketamine may also have less abuse potential than S- ketamine.



Study Design

Double-blind, randomized, placebo-controlled, multicenter, multiregion study, comprised of 3 phases:

- screening (up to 2 weeks)
- in-patient treatment (Day -1 to Day 2)
- post-treatment follow-up (7 and 14 days after infusion).

The study consisted of 3 arms: placebo, PCN-101 30 mg, and PCN- 101 60 mg, all given as an i.v. infusion over 40 minutes.

A planned total of 93 adult subjects with TRD were randomly allocated in equal cohorts of 31 subjects/arm to the 3 arms of the study in a blinded manner.

The primary endpoint was a change on the MADRS from pre dose to 24 hours post dose.

Key Inclusion & Exclusion Criteria

- **Patients with MDD (confirmed by MINI)**
- **Inadequate response to >/= 2 antidepressants for >/= 6 weeks**
- **Stable antidepressant regimen without dose change for 30 days**
- **No major medical or psychiatric co-morbidities**

Subject Disposition

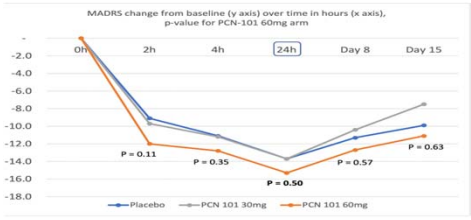
Screened: 132
Randomized: 102
PBO: 34,
PCN-101 30mg 33,
PCN-101 60mg: 35
Completers
PBO: 31
PCN-101 30mg: 31
PCN-101 60 mg 31

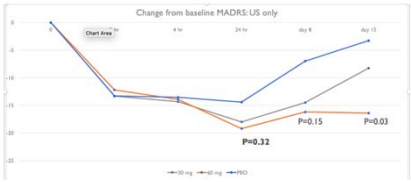
Baseline demographics
Age: (mean): 44.9
Sex: Male 40%; Female: 60%
Region: USA: 27%, Europe: 73%
MADRS Score baseline: 29.7

Results

Primary Endpoint

Analysis timepoint	Treatment Arm	Adj mean (SE)	Diff adj mean (SE) PCN-101– PBP (95% CI)	P- value
Day 1, 24 hrs	PCN-101 30 mg (N=33)	-13.7 (1.75)	-0.0 (2.42) [-4.84, 4.77]	0.9886
	PCN-101 60 mg (N=35)	-15.3 (1.69)	-1.6 (2.38) [-6.35, 3.11]	0.4988
	PBO (N=33)	-13.7 (1.76)	---	---





Responder and Sustained Responder

Response: at least 50% change from baseline

Sustained Responder: Response at 24 hrs continued to day 15

Treatment	N	Responder (24 hrs)	Sustained Responder (Day 15)	Adj Odds ratio	P-value	Sus Resp / Responder Ratio
PCN-101 30 mg	33	19 (57.6%)	4 (12.1%)	0.976 (0.22, 4.32)	0.97	21%
PCN 101 60 mg	35	16 (45.7%)	10 (28.6%)	2.863 (0.79, 10.37)	0.10	62.5%
PBO	33	16 (48.5%)	4 (12.1%)			25%

Efficacy conclusions

- Primary endpoint for efficacy not met
- Regional differences in efficacy with significant difference at day 15

Safety

	PBO	PCN-101 30 mg	PCN-101 60mg	Total
No of TEAE's	**44**	**22**	**53**	**119**
Subjects with Any TEAE	**18 (53)**	**11 (33)**	**18 (51)**	**47 (46)**
Nervous System	**15 (44)**	**9 (27)**	**14 (40)**	**38 (37)**
Somnolence	9 (26)	4 (12)	4 (11)	17 (17)
Dizziness	5 (15)	2 (6)	7 (20)	14 (14)
Headache	3 (9)	3 (9)	2 (6)	8 (8)
Dysarthria	0 (0)	0 (0)	2 (6)	2 (2)
Psychiatric disorders	**5 (15)**	**4 (12)**	**5 (14)**	**14 (14)**
Derealization	4 (12)	4 (12)	3 (9)	11 (11)
GI Disorders	**2 (6)**	**0 (0)**	**5 (14)**	**7 (7)**
Nausea	1 (3)	0 (0)	3 (9)	4 (4)
General disorders	1 (3)	1 (3)	4 (11)	6 (6)
Feeling drunk	0 (0)	0 (0)	2 (6)	2 (2)

	PCN-101 30 mg	PCN-101 60 mg	Placebo	Total
No of subjects with at least one post baseline MOASS or CADSS assessment	33	35	33	101
Subjects with post baseline MOASS <5	9 (27.3)	12 (34.3)	11 (33.3)	32 (31.7)
Subjects with post baseline CADSS >4 and change from baseline >0	12 (36.4)	8 (22.9)	9 (27.3)	29 (28.7)

Safety conclusions

- Dissociation and sedation similar to placebo
- Well tolerated at all doses and timepoints

Conclusions

60 mg dose showed a non-significant but consistent improvement (1.2 – 2.9 points vs placebo) on the MADRS across all timepoints.

- *Placebo effect was higher than usually observed in TRD studies*
- *Regional differences in efficacy were also observed with the US demonstrating a treated drug-placebo difference which was statistically significant at day 15*

Consistent signals were seen in both the remission rate and in the sustained responder analyses of an effect at 60 mg

Overall Safety Profile:

- *PCN-101 was well tolerated at all doses and timepoints*
- *Sedation and dissociation were seen at very low rates comparable to placebo*
- *No clinically significant findings in labs, or ECG's*
- *Mean PBO corrected blood pressure changes were less than 5 mm Hg*

References

1. Zhang J, Yao W, Hashimoto K. Arketamine, a new rapid-acting antidepressant: A historical review and future directions. Neuropharmacology. 2022 Nov 1;218:109219.
2. Yang C et. al. R-ketamine: a rapid-onset and sustained antidepressant without psychotomimetic side effects. Translational Psychiatry, 2015, volume 5, page 632

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