Poster #18

KET01-02: Oral Prolonged-Release Adjunctive KET01 Ketamine for Treatment-Resistant Depression. Results of a Randomized Placebo-Controlled Double-Blind Phase 2 Trial

KETABON

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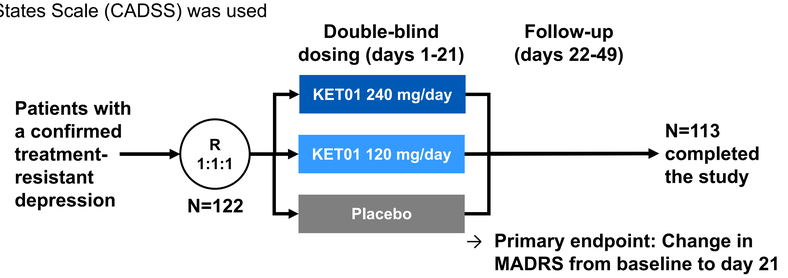
BACKGROUND

Approximately one-third of patients with major depressive disorder fail to respond to two or more adequately administered antidepressant regimens and are deemed "treatment resistant". Ketamine is a rapid-acting antidepressant; however, its use is associated with dissociative and cardiovascular adverse effects. KET01 is an oral prolonged-release formulation of racemic ketamine in development for treatment-resistant depression with early data indicating a low potential for dissociation.

PATIENTS AND METHODS

KET01-02 (EudraCT ID: 2021-004927-34) was a randomized placebo-controlled double-blind phase 2 trial in adult patients with treatment-resistant depression. Outpatients were randomized to once-daily placebo, 120 mg KET01, or 240 mg KET01, for three weeks. The first dose was administered under supervision; the remaining doses were taken at home. Primary endpoint was mean change from baseline in the Montgomery-Åsberg Depression Rating Scale (MADRS) on Day 21 (mixed model for repeated measures). Clinician-Administered Dissociative States Scale (CADSS) was used



RESULTS

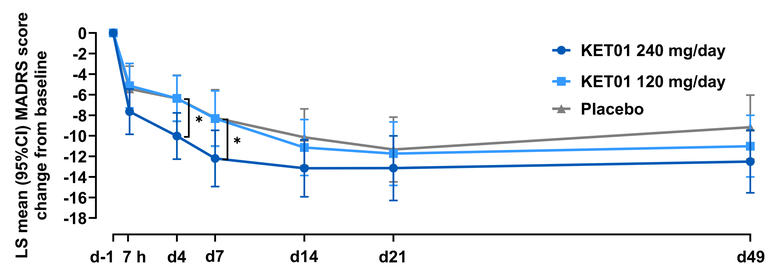
122 patients were randomized to 120 mg/day (n=42) or 240 mg/day KET01 (n=40), or to placebo (n=40). Median age was 41 years (range: 19-65). 72 (59%) patients were female, 53 of them (73.6%) were of childbearing potential. Baseline characteristics were balanced between the trial groups.

Baseline Characteristics	KET01 240 mg (n=40)	KET01 120 mg (n=42)	Placebo (n=40)	Total (n=122)
Age in years, median (range)	40 (21-64)	41 (19-65)	40 (19-58)	41 (19-65)
Female, n (%)	24 (60.0)	27 (64.3)	21 (52.5)	72 (59.0)
Childbearing potential, n (%)	17 (70.8)	20 (74.1)	16 (76.2)	53 (73.6)

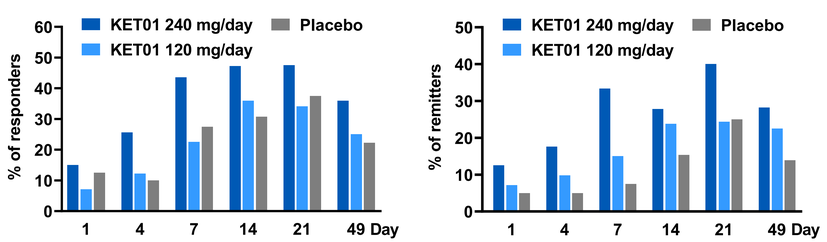
MAIN TAKEAWAY

- **Oral treatment with 240 mg/day KET01 induced a rapid and clinically relevant reduction of depressive symptoms which were maintained over the 4-week follow-up.**
- **Anti-depressive doses of KET01 were associated with minimal signs of dissociative symptoms (potentially due to a combination of low plasma ketamine levels and high concentration of hydroxynorketamine).**

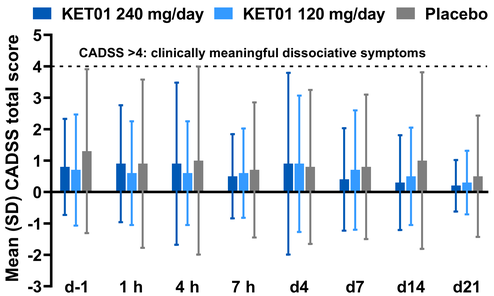
240 mg/day KET01 dose demonstrated rapid improvements in MADRS at 7 hours after the first dosing (least squares mean change from baseline: -7.65; Δ vs placebo: -2.22, n.s., see below) with statistically significant separation on Day 4 (mean change: -10.02; Δ vs placebo: -3.66, p=.020), and Day 7 (mean change: -12.21; Δ vs placebo: -3.95, p=.042). Although the primary efficacy endpoint was not met, the improvements were sustained until Day 21 (mean change: -13.15; Δ vs placebo: -1.82, n.s.) and after 4 additional weeks of follow-up (mean change: -12.51; Δ vs placebo: -3.35, n.s.).



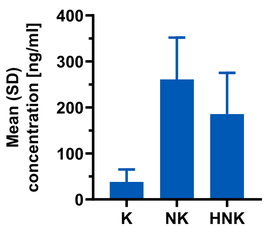
Clinical response rates (≥50% MADRS score improvement) at Day 21 in the 240 mg/day, 120 mg/day KET01, and placebo group were 47.5%, 34.1%, and 37.5% respectively; remission rates (MADRS score ≤10) were 40.0%, 24.4%, and 25.0%, respectively (see below).



There was no difference in the mean CADSS scores between the groups at any time point (see to the right). CADSS total score >4 after baseline and >0 increase from baseline (indicating potentially clinically relevant dissociative symptoms) was observed in 15%, 12%, and 10% of patients in the 240 mg/day, 120 mg/day KET01, and placebo groups, respectively.



At 7 hours after the first KET01 dose (240 mg, close to the presumed C_{max} of ketamine) observed mean concentrations in plasma were 37.7 ng/ml for ketamine (K), 260.6 ng/ml for norketamine (NK), and 185.3 ng/ml for hydroxynorketamine (HNK, see to the right). Plasma concentrations of ketamine appeared lower while concentrations of metabolites norketamine and hydroxynorketamine appeared higher than reported for intravenous infusions of 0.5 mg/kg of ketamine hydrochloride (Farmer at al., *Neuropsychopharmacology*. 2020 Jul; 45(8): 1398–1404.)



KET01 was well tolerated with treatment-emergent adverse events (TEAE) reported by 47.5%, 50.0%, and 62.5% in the placebo, 120 mg/day, and 240 mg/day KET01 groups, respectively (see below for most frequent TEAEs). Serious TEAEs included suicidal depression in one patient (2.5%) in the KET01 240 mg/day group and suicidal ideation in one patient (2.4%) in the KET01 120 mg/day group. Transient elevations in mean plasma gamma-glutamyltransferase and alanine aminotransferase concentrations occurred from week 2 for both KET01 groups.

Preferred term, N (%)	KET01 240 mg (n=40)	KET01 120 mg (n=42)	Placebo (n=40)
Dizziness	7 (17.5)	2 (4.8)	1 (2.5)
Headache	4 (10.0)	5 (11.9)	7 (17.5)
Hepatic enzyme increased	4 (10.0)	1 (2.4)	0 (0.0)
Dissociation	4 (10.0)	0 (0.0)	0 (0.0)
Cystitis	3 (7.5)	1 (2.4)	0 (0.0)

The KET01-02 trial was conducted by Ketabon GmbH, a joint venture by HMNC Brain Health and Develco Pharma Schweiz AG.