Poster #3 KET01-03: A Randomized, Placebo-Controlled, Double-Blind, Double-Dummy, Cross-Over Phase 1 Trial to Assess the Tolerability, Safety, and Pharmacokinetics of Antidepressant Doses of Oral Ketamine Hydrochloride Prolonged Release Tablets (KET01) Compared to Intranasal Esketamine in Healthy Male Subjects

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BACKGROUND

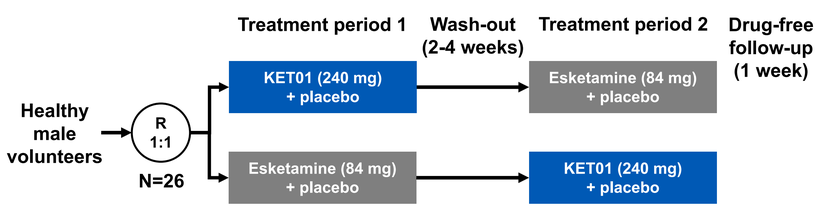
Sub-anesthetic doses of ketamine and esketamine exert rapid antidepressant effects. Acute side effects, e.g., dissociation and increase in blood pressure have been observed frequently after several routes of administration of ketamine-based medications, and are related to peak plasma levels. Systemic or oral immediate-release administration of ketamine or esketamine lead to early C_{max} values accompanied by dissociation and blood pressure changes. Administration of an oral prolonged-release formulation of ketamine results in relatively lower C_{max} and relatively higher concentrations of the metabolite hydroxynorketamine, compared to after rapid systemic administration. Hydroxynorketamine has shown efficacy in rodent models of depression.

The objective of the KET01-03 trial was to compare the tolerability and safety of single antidepressant doses of oral KET01 and intranasal esketamine, and to investigate the pharmacokinetics of KET01 and esketamine and their main metabolites.

PARTICIPANTS AND METHODS

KET01-03 was a randomized, placebo-controlled, double-blind, double-dummy, single-center, cross-over phase 1 trial in healthy male volunteers. Subjects were randomized to KET01 (240 mg prolonged-release ketamine) and esketamine (84 mg SPRAVATO®; active comparator; the highest approved starting dose). Two single-dose treatment periods were separated by a wash-out period of 14 to 28 days.

The primary objective was to compare the maximum changes in the Clinician-Administered Dissociative States Scale (CADSS) score within the first 24 h after administration of the trial treatment. Additionally, CADSS was assessed at 40 min and 6 h 30 min after treatment, presumed to coincide with C_{max} values for esketamine and KET01, respectively.



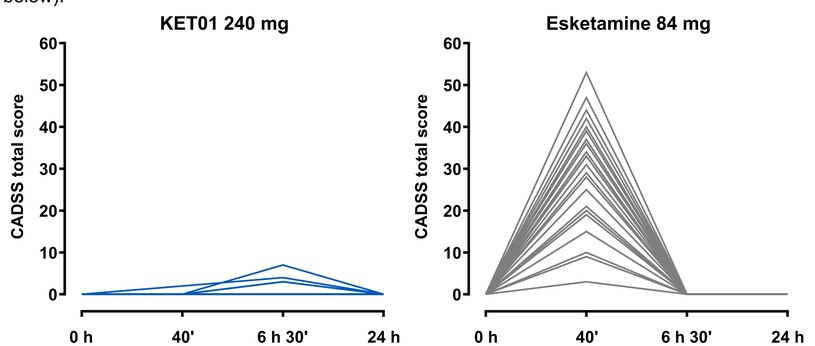
RESULTS

26 subjects were included in the trial between July and August 2023. Median age was 29 years (range: 25-44) in the KET01-esketamine and 35 (range: 21-45) in the esketamine-KET01 group. 26 subjects completed treatment phase 1, 25 completed treatment phase 2 (one subject in KET01-esketamine group discontinued treatment due to physician's decision).

MAIN TAKEAWAY

- **KET01 had minimal dissociative effects at antidepressant dose (240 mg), in contrast to esketamine (84 mg).**
- **KET01 had minimal effects on heart rate and blood pressure during the first 10 hours after treatment as opposed to a rapid, transient increase following esketamine treatment.**

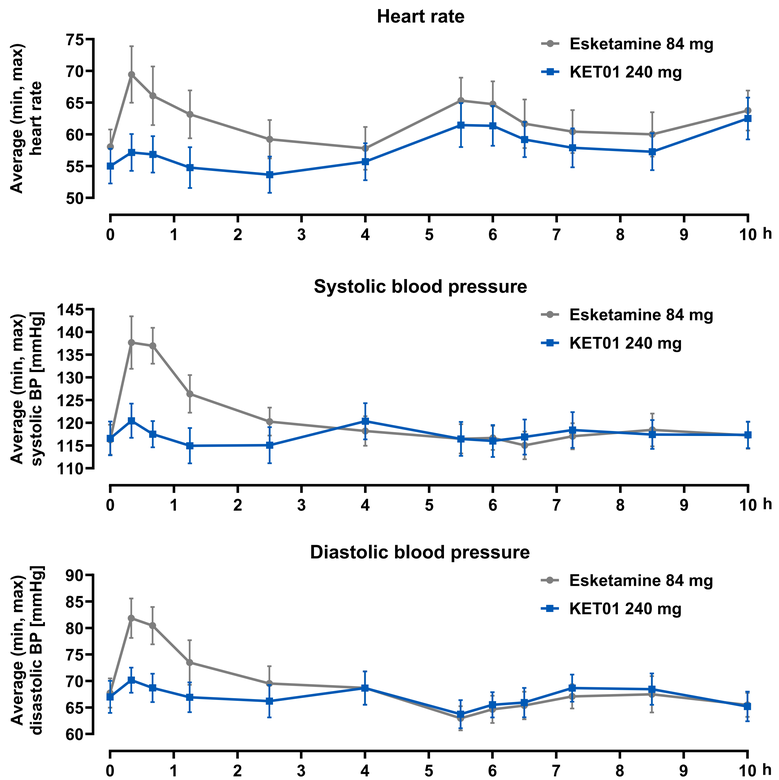
CADSS total scores (sum of the 23 items) remained stable throughout the first 24 h after KET01 treatment, with only 4 subjects (15.4%) with CADSS score >0. In contrast, esketamine induced a pronounced CADSS score increase at 40 min after treatment in most subjects, with CADSS score >0 during the first 24 h in all subjects (see figure below). In the primary endpoint analysis, maximum change in CADSS score after baseline was lower after KET01 than after esketamine in both treatment periods; mean maximum change in CADSS score after KET01 treatment was lower by 29.01 (SD=2.35; p<.00000000001) than after esketamine (see table below).



Mean (SD) maximum change in CADSS	KET01 (240 mg)	Esketamine (84 mg)	Treatment difference (CADSS score): KET01 – esketamine
Treatment period 1	0.31 (1.11)	32.17 (8.05)	-31.83 (7.78)
Treatment period 2	1.00 (2.12)	27.15 (15.48)	-26.15 (14.79)
Treatment periods combined			-29.01 (2.35); p<.00000000001

In the accompanying poster (#18), we report mean plasma concentrations of ketamine (37.7 ng/ml), norketamine (260.6 ng/ml), and hydroxynorketamine (185.3 ng/ml) at 7 h after KET01 treatment (240 mg) in the KET01-02 trial.

KET01 treatment was associated with a slight increase in heart rate observed from 5 h 30 min, and minor fluctuations in blood pressure. In contrast, esketamine included a rapid (within the first 20 min) increase in average heart rate and blood pressure (see below). Average heart rate and blood pressure peaked at 40 min after esketamine administration, coinciding with the presumed C_{max} for esketamine, and thereafter declined to follow a profile parallel to that of KET01 from 4 hours after dosing. No serious adverse events were reported.



The KET01-03 trial was conducted by Ketabon GmbH, a joint venture by HMNC Brain Health and Develco Pharma Schweiz AG.