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SAFETY AND PHARMACOKINETICS STUDY OF INHALED ESKETAMINE AFTER A SINGLE DOSE IN HEALTHY VOLUNTEERS

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This study was supported by The National Centre for Research and Development (POIR 1/1.1.1).

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INTRODUCTION

Ketamine is a medicine used for over 50 years in human and veterinary anesthesia and analgesia. Esketamine is a ketamine enantiomer showing 3- to 4- fold greater affinity to NMDA receptors than R-enantiomer. Recently, it was demonstrated that ketamine significantly and rapidly attenuates depressive symptoms in patients suffering from treatment-resistant depression (TRD) [1], [2] as well as reduces the intensity of suicidal thoughts [3]. In most clinical trials involving patients with TRD, ketamine is used either as a racemic mixture for intravenous administration or as an intranasally administered S-enantiomer. Oral administration is not considered a promising route of drug delivery due to ketamine's extensive first-pass metabolism effect. Inhaled Esketamine represents a new approach that may provide additional advantages over currently used/above described administration routes. The presented study determines the pharmacokinetic properties of Esketamine delivered from dry powder inhaler (DPI) and assess its safety when inhaled.

MATERIALS AND METHODS

Study design

- This was a one-centre, open label, two part, single-ascending dose study in healthy volunteers.
- In PART A of the study subjects performed 1-6 consecutive inhalations, called an inhalation event. There were 6 cohort (n=3/cohort).
- In PART B of the study subjects performed a dosing sequence: 3 inhalation events spread over 30 minutes (3-12 inhalations totally) (Fig.1.). There were 4 cohorts (n=3/cohort).

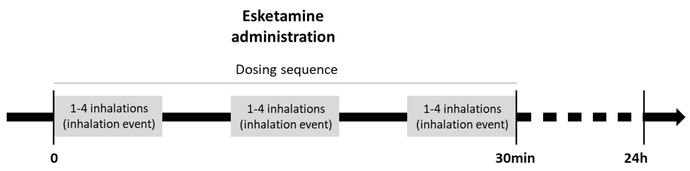

Fig.1. Dosing sequence scheme performed in PART B of the study.

Study population

- 18 healthy volunteers (18-55 years old), non-smokers, who met all the inclusion and none of the exclusion criteria were enrolled for PART A of the study.
- 12 healthy volunteers (18-55 years old), non-smokers, who met all the inclusion and none of the exclusion criteria were enrolled for PART B of the study.

Investigational Medicinal Product (IMP)

- IMP contained esketamine hydrochloride as an active pharmaceutical ingredient, inhalation powder delivered by dry powder inhaler (DPI).
- One inhalation of IMP contained 4.6 mg of esketamine hydrochloride (4 mg of esketamine free base) and excipients: lactose monohydrate and magnesium stearate.

Pharmacokinetics

- Blood samples for PK analysis, in each part, were collected in time-points: predose (≤ 1h before the IMP administration), 2, 4, 6, 10, 15, 20, 25, 30, 35, 40, 45 min and 1, 2, 6, 12, 24 hours after the start of dosing.
- Esketamine and Esnorketamine concentration measurements were performed in human EDTA K_2 plasma samples using UPLC/MS/MS racemic method.

Safety evaluation

- Safety assessments included: adverse events (AE) reporting, clinical laboratory tests (haematology, blood chemistry, urinalysis), vital signs measurements, physical examination, electrocardiography (ECG).

Questionnaire

- The questionnaire the subject answered to rate potential unusual feelings and impressions allowing for IMP psychoactive side effects assessments were completed during both parts of the study.

Statistics

- Demographic data was analysed descriptively.
- PK parameters were derived individually for each subject and computed using a non-compartmental modelling approach. PK parameters were analysed with descriptive summary statistics (incl. mean and coefficient of variation). Esketamine and Esnorketamine time-course plasma concentration profile of all subjects and mean for each cohort were determined.
- Adverse events and symptoms reported through subject's questionnaire were evaluated descriptively.

RESULTS

DEMOGRAPHICS

Tab.1. Demographic data by sex of PART A subjects.

	Age [years]	Height [cm]	Weight [kg]	BMI [kg/m²]
Males				
N	11	11	11	11
Mean	33.8	179.8	80.9	25.1
SD	7.5	7.7	10.9	3.2
Median	34.0	178.0	80.7	24.8
Min	21	168	65.7	18.58
Max	47	192	106	29.33
Females				
N	7	7	7	7
Mean	38.7	164.1	61.1	22.6
SD	10.5	2.5	6.6	1.9
Median	44.0	163.0	61.3	23.1
Min	21	161	52.8	20.36
Max	48	168	72.6	25.72

Tab.2. Demographic data by sex of PART B subjects.

	Age [years]	Height [cm]	Weight [kg]	BMI [kg/m²]
Males				
N	6	6	6	6
Mean	33.2	180.3	84.6	25.9
SD	7.9	6.3	11.2	2.2
Median	30.5	180.0	81.5	25.8
Min	26	172	76.5	23.61
Max	47	190	107	29.64
Females				
N	6	6	6	6
Mean	35.7	161.0	65.0	25.1
SD	11.8	3.8	7.7	2.8
Median	36.5	160.0	62.2	25.0
Min	20	156	56	22.15
Max	49	166	75.5	29.49

ADVERSE EVENTS

All adverse events observed in PART A and PART B of the study are shown in Tab.3. and Tab.4.

In PART A abdominal pain (2 events), headache (3 events), herpex simplex (1 event), fainting (1 event) were classified by PI as not related to the IMP.
In PART B headache (1 event) was classified by PI as not related to the IMP.

Tab. 3. Adverse events observed in PART A of the study

AE description	AE observed (N(%))	Subjects affected (N(%))
abdominal pain	2 (8.3%)	2 (11.1%)
dizziness	7 (29.2%)	7 (38.9%)
fainting	1 (4.2%)	1 (5.6%)
fatigue	2 (8.3%)	2 (11.1%)
headache	4 (16.7%)	3 (16.7%)
herpes simplex	1 (4.2%)	1 (5.6%)
hypertension	4 (16.7%)	4 (22.2%)
sleepiness	1 (4.2%)	1 (5.6%)
sweating increased	1 (4.2%)	1 (5.6%)
tremor	1 (4.2%)	1 (5.6%)
Total	**24 (100.0%)**	**18 (100.0%)**

Tab. 4. Adverse events observed in PART B of the study

AE description	AE observed (N(%))	Subjects affected (N(%))
concentration disorders	3 (8.1%)	2 (16.7%)
cough	1 (2.7%)	1 (8.3%)
disorders in time perception	1 (2.7%)	1 (8.3%)
dizziness	9 (24.3%)	7 (58.3%)
feeling of a heavy head	3 (8.1%)	1 (8.3%)
feeling of anxiety	1 (2.7%)	1 (8.3%)
feeling of calmness and relaxation	1 (2.7%)	1 (8.3%)
feeling of hot feet	1 (2.7%)	1 (8.3%)
feeling of relaxation	9 (24.3%)	4 (33.3%)
feeling of uncertainty	1 (2.7%)	1 (8.3%)
headache	3 (8.1%)	3 (25.0%)
sleepiness	1 (2.7%)	1 (8.3%)
sweating of feet and hands	1 (2.7%)	1 (8.3%)
sweaty hands	1 (2.7%)	1 (8.3%)
vomiting	1 (2.7%)	1 (8.3%)
Total	**37 (100.0%)**	**12 (100.0%)**

QUESTIONNAIRE

Tab. 5. Symptoms reported during PART A and PART B of the study through patients questionnaire.

AE description	PART A		PART B	
	AE observed (N(%))	Subjects affected (N(%))	AE observed (N(%))	Subjects affected (N(%))
lack of concentration	3 (18.8%)	3 (16.7%)	4 (12.5%)	4 (33.3%)
lack of physical coordination	1 (6.2%)	1 (5.6%)	2 (6.2%)	2 (16.7%)
excessive cheerfulness, emotional instability	0 (0.0%)	0 (0.0%)	3 (9.4%)	3 (25.0%)
auditory symptoms, i.e. auditory hallucinations, e.g. hearing voices, sounds unrelated to the surrounding reality, etc.	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
visual symptoms, i.e. visual hallucinations, visual disturbances, spreading of contours and/or sharpness, color vision disturbance, etc.	3 (18.8%)	3 (16.7%)	2 (6.2%)	2 (16.7%)
the feeling of being outside of your own body	0 (0.0%)	0 (0.0%)	2 (6.2%)	2 (16.7%)
the feeling of time disorders - time flows slower or faster	1 (6.2%)	1 (5.6%)	2 (6.2%)	2 (16.7%)
sense of self-unreality, depersonalization	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (8.3%)
excitement, anxiety, irritability	1 (6.2%)	1 (5.6%)	2 (6.2%)	2 (16.7%)
strong unjustified anxiety or fear	0 (0.0%)	0 (0.0%)	1 (3.1%)	1 (8.3%)
feeling of being ‚high'	2 (12.5%)	2 (11.1%)	5 (15.6%)	5 (41.7%)
feeling of paranoia, i.e. presence of thoughts and/or illusions about the absurd content, e.g. unreasonable feeling that someone is watching you/following you	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
delusions, i.e. false thoughts that are not properly assessed, e.g. you seem to be someone else	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
dizziness, nausea	5 (31.2%)	5 (27.8%)	8 (25.0%)	8 (66.7%)
Total	**16 (100.0%)**	**18 (100.0%)**	**32 (100.0%)**	**12 (100.0%)**

PHARMACOKINETICS

PART A

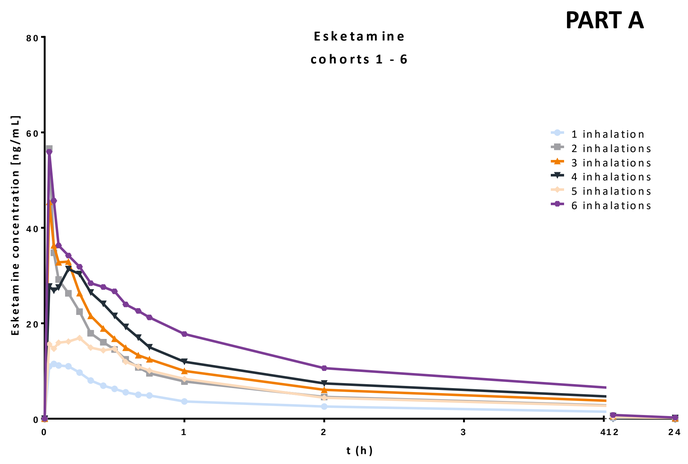

Fig.2. Mean Esketamine's time-course plasma concentration profile for cohorts from PART A of the study.

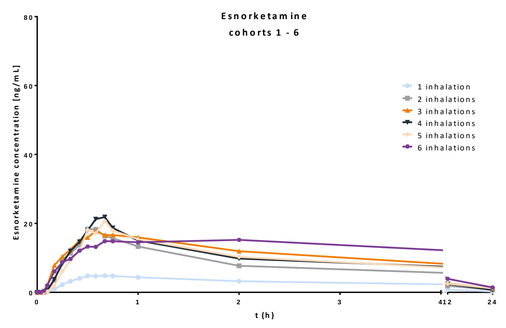

Fig.3. Mean Esnorketamine's time-course plasma concentration profile for cohorts from PART A of the study.

Representative pharmacokinetic parameters for Esketamine and Esnorketamine from PART A of the study are shown in Tab.6. and Tab.7.

Tab.6. Esketamine's pharmacokinetic parameters from PART A of the study.

Cohort	N	C_{max} [ng/mL]		T_{max} [h]		AUC_{0-24} [ng/mL*h]	
		Mean	CV	Mean	CV	Mean	CV
1	3	11.87	36.61%	0.11	45.83%	17.91	51.71%
2	3	59.49	100.45%	0.08	98.97%	40.38	38.51%
3	3	45.44	23.08%	0.03	0.00%	52.68	20.61%
4	3	36.47	56.71%	0.08	98.97%	61.77	95.41%
5	3	17.37	135.74%	0.18	70.36%	37.55	146.75%
6	3	55.93	90.39%	0.03	0.00%	83.51	65.37%

Tab.7. Esnorketamine's pharmacokinetic parameters from PART A of the study.

Cohort	N	C_{max} [ng/mL]		T_{max} [h]		AUC_{0-24} [ng/mL*h]	
		Mean	CV	Mean	CV	Mean	CV
1	3	5.12	41.30%	0.61	20.83%	29.60	49.22%
2	3	19.9	62.11%	0.47	20.38%	77.34	66.64%
3	3	20.17	38.33%	1.08	73.38%	104.18	12.32%
4	3	22.36	70.66%	0.58	14.29%	96.97	57.92%
5	3	20.90	148.12%	0.58	14.29%	96.07	146.20%
6	3	16.64	53.37%	1.50	57.74%	146.13	78.48%

PART B

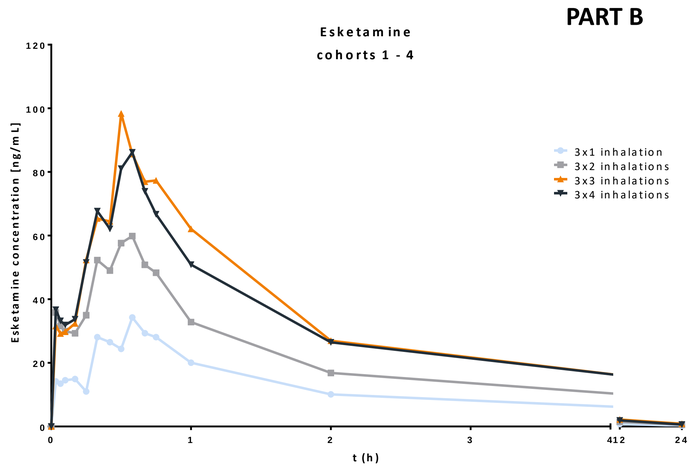

Fig.4. Mean Esketamine's time-course plasma concentration profile for cohorts from PART B of the study.

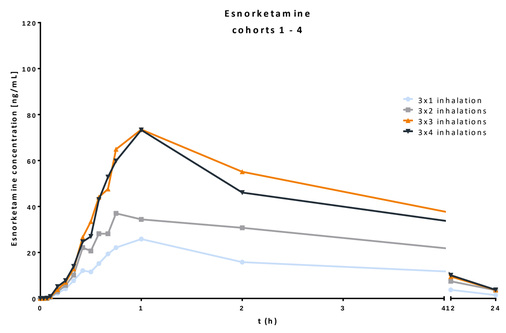

Fig.5. Mean Esnorketamine's time-course plasma concentration profile for cohorts from PART B of the study.

Representative pharmacokinetic parameters for Esketamine and Esnorketamine from PART B of the study are shown in Tab.8. and Tab.9.

Tab.8. Esketamine's pharmacokinetic parameters from PART B of the study.

Cohort	N	C_{max} [ng/mL]		T_{max} [h]		AUC_{0-24} [ng/mL*h]	
		Mean	CV	Mean	CV	Mean	CV
1	3	34.86	48.36%	0.61	20.83%	78.60	15.03%
2	3	62.84	35.91%	0.50	16.67%	138.61	36.29%
3	3	105.71	54.57%	0.61	20.83%	216.51	8.83%
4	3	88.74	11.25%	0.50	33.33%	203.78	23.39%

Tab.9. Esnorketamine's pharmacokinetic parameters from PART B of the study.

Cohort	N	C_{max} [ng/mL]		T_{max} [h]		AUC_{0-24} [ng/mL*h]	
		Mean	CV	Mean	CV	Mean	CV
1	3	25.86	35.79%	1.00	0.00%	146.49	2.86%
2	3	41.28	17.78%	1.25	52.92%	268.48	9.57%
3	3	75.98	24.29%	1.25	52.92%	419.71	9.01%
4	3	73.38	25.31%	0.89	21.65%	406.96	13.91%

SUMMARY AND CONSLUSIONS

- Inhaled Esketamine was well tolerated with no serious AEs.
- Most reported adverse events were classified as mild and few were classified as moderate.
- Most frequently reported AE related or possibly related to IMP were dizziness, feeling of relaxation, hypertension and concentration disorders.
- Symptoms reported through questionnaire may suggest possible psychoactive (psychomimetic/dissociative) symptoms after administered doses of Esketamine, in some subjects.
- The safety profile of Esketamine during the study did not differ from literature data.
- Pharmacokinetic profile of inhaled Esketamine supports dry powder inhalation as a delivery route.
- The study results justify further development of inhaled Esketamine in patients suffering from treatment–resistant depression (TRD).

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Presented at 31st ECNP Congress, October 8, 2018