P.164

SAFETY AND PHARMACOKINETIC STUDY OF INHALED ESKETAMINE AFTER A MULTIPLE DOSE IN HEALTHY VOLUNTEERS

S. Janowska[1], E. Tratkiewicz[2], M. Matloka[2], P. Perko[2], M. Gaciarz[2], M. Wieczorek[1,2]

1 Celon Pharma SA, Clinical Department, Lomianki, Poland
2 Celon Pharma SA, R&D Centre, Lomianki, Poland

corresponding author: sylwia.janowska@celonpharma.com

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INTRODUCTION

Ketamine is a medicine used for over 50 years in human and veterinary anaesthesia and analgesia. Esketamine is a ketamine enantiomer showing 3- to 4- fold greater affinity to NMDA receptors than R-enantiomer. Several clinical studies with both single and multiple administrations have demonstrated the rapid antidepressant effect of ketamine in patients suffering from depression, mostly with treatment-resistant depression (TRD), as well as reducing the intensity of suicidal thoughts [1, 2, 3, 4]. In those studies ketamine was used as a racemic mixture in intravenous 40 minute infusion or as an intranasal application of the S-enantiomer. Inhaled Esketamine represents a new approach. Recently we demonstrated the pharmacokinetic properties and safety of Esketamine delivered from dry powder inhaler (DPI) after a single dose in healthy volunteers [5]. The present study was intended to determine the pharmacokinetic properties and safety of Esketamine after multiple administration via dry powder inhalation.

MATERIALS AND METHODS

Study design

- This was a one-centre, randomized, double-blind, placebo controlled, multiple ascending dose study in healthy volunteers.
- Participants underwent one cycle of treatment: 4 doses twice a week over 2 week period (Day 1, 4, 8 and 11). A single dose was defined as a dosing sequence consisting of 3 inhalation events spread over 30 minutes (3-12 inhalations in total) (Fig.1.). There were 4 cohorts (n = 8/ cohort) with randomization 3:1.

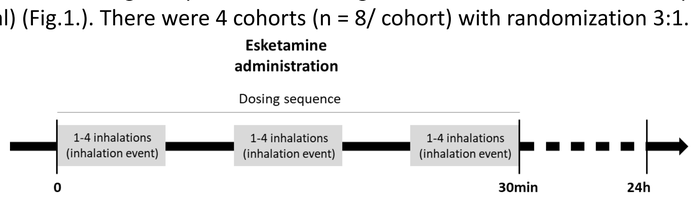

Fig.1. Dosing sequence scheme.

Study population

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

* Total number of subjects (N=33) is due to the fact that, in cohort receiving PG061, one subject withdrew from the study after two doses due to personal reasons so second subject was recruited to replace him. The replacing subject also withdrew from the study after second dose due to personal reasons. Results observed for those two subjects were included into the analysis.

Investigational Medicinal Product (IMP)

- IMP contained esketamine hydrochloride as an active pharmaceutical ingredient, and was in the form of 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.
- Placebo contained lactose monohydrate and magnesium stearate as an inhalation powder delivered by DPI.

Pharmacokinetics

- Blood samples for PK analysis were collected at the following 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 following the start of each dosing sequence.
- 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 participant answered to rate potential unusual feelings and impressions allowing for IMP psychoactive side effects assessments were completed during the study.

Statistics

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

RESULTS

DEMOGRAPHICS

Tab.1. Demographic data by sex.

	Age [years]	Height [cm]	Weight [kg]	BMI [kg/m²]
Males				
N	22	22	22	22
Mean	35.1	177.9	78.5	24.8
SD	9.7	7.2	9.4	2.6
Median	33.5	176.3	79.0	24.38
Min	18	166	61.5	19.85
Max	52	194	100	29.59
Females				
N	11	11	11	11
Mean	36.9	165.8	69.5	25.3
SD	10.0	7.7	8.5	2.8
Median	41.0	165.0	70.0	24.58
Min	21	154	52	21.55
Max	49	177	86	29.73

ADVERSE EVENTS - TOTAL

Tab.2. Total number of AEs by dose, intensity and relationship to the study IMP.

Total		N=199	
Dose [No. of inhalations in one dose]	3	46	23.1%
	6	40	20.1%
	9	29	14.6%
	12	83	41.7%
	Placebo	1	0.5%
Intensity	Mild	188	94.5%
	Moderate	11	5.5%
	Severe	0	0.0%
Relationship to the study IMP	Not related	13	6.5%
	Possible related	20	10.1%
	Related	166	83.4%

QUESTIONNAIRE

Tab. 3. Symptoms reported through participant questioannaire.

AE description	AE observed (N(%))	Subjects affected (N(%))
lack of concentration	24 (12.6%)	12 (36.4%)
lack of physical coordination	13 (6.8%)	9 (27.3%)
excessive cheerfulness, emotional instability	5 (2.6%)	4 (12.1%)
auditory symptoms, i.e. auditory hallucinations, e.g. hearing voices, sounds unrelated to the surrounding reality, etc	4 (2.1%)	4 (12.1%)
visual symptoms, i.e. visual hallucinations, visual disturbances, spreading of contours and/or sharpness, color vision disturbance, etc.	14 (7.4%)	8 (24.2%)
the feeling of being outside of your own body	1 (0.5%)	1 (3.0%)
the feeling of time disorders - time flows slower or faster	16 (8.4%)	9 (27.3%)
sense of self-unreality, depersonalization	5 (2.6%)	3 (9.1%)
excitement, anxiety, irritability	9 (4.7%)	5 (15.2%)
strong unjustified anxiety or fear	5 (2.6%)	4 (12.1%)
feeling of being faded	38 (20.0%)	16 (48.5%)
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%)
delusions, i.e. false thoughts that are not properly assessed, e.g. you seem to be someone else	1 (0.5%)	1 (3.0%)
dizziness, nausea	55 (28.9%)	19 (57.6%)
Total	**190 (100.0%)**	**33 (100.0%)***

ADVERSE EVENTS - DETAILES

Tab. 4. Adverse events observed during the study.

AE description	AE observed (N(%))	Subjects affected (N(%))
acute hearing	1 (0.5%)	1 (3.0%)
blurred vision	1 (0.5%)	1 (3.0%)
bruise on the crook of elbow	2 (1.0%)	2 (6.1%)
buzzing sound inside head	1 (0.5%)	1 (3.0%)
concentration disorders	3 (1.5%)	3 (9.1%)
coordination disorders	1 (0.5%)	1 (3.0%)
diarrhoea	2 (1.0%)	2 (6.1%)
disorders in temperature perception	1 (0.5%)	1 (3.0%)
disorders in time perception	6 (3.0%)	3 (9.1%)
disorders in pain perception	1 (0.5%)	1 (3.0%)
dizziness	84 (42.2%)	19 (57.6%)
face muscle stiffness	1 (0.5%)	1 (3.0%)
fainting	2 (1.0%)	2 (6.1%)
fatigue	1 (0.5%)	1 (3.0%)
feeling of cold hands	1 (0.5%)	1 (3.0%)
feeling of clogging ears	1 (0.5%)	1 (3.0%)
feeling of disorientation	1 (0.5%)	1 (3.0%)
feeling of indifference	1 (0.5%)	1 (3.0%)
feeling of relaxation	21 (10.6%)	11 (33.3%)
feeling of stupefaction	8 (4.0%)	4 (12.1%)
headache	11 (5.5%)	5 (15.2%)
hematoma on the eyelid	1 (0.5%)	1 (3.0%)
hypertension	8 (4.0%)	6 (18.2%)
lack of eye concentration	1 (0.5%)	1 (3.0%)
nausea	2 (1.0%)	1 (3.0%)
numbness of arms and legs	1 (0.5%)	1 (3.0%)
numbness of face	2 (1.0%)	2 (6.1%)
numbness of feet	1 (0.5%)	1 (3.0%)
numbness of the mouth	12 (6.0%)	5 (15.2%)
numbness of the tongue	10 (5.0%)	7 (21.2%)
nystagmus	2 (1.0%)	1 (3.0%)
redness of the neck	1 (0.5%)	1 (3.0%)
sleepiness	2 (1.0%)	2 (6.1%)
sweating increased	1 (0.5%)	1 (3.0%)
tingling of the mouth	1 (0.5%)	1 (3.0%)
tinnitus	2 (1.0%)	1 (3.0%)
vomiting	1 (0.5%)	1 (3.0%)
Total	**199 (100.0%)**	**33 (100.0%)***

Most frequently reported AE related or possibly related to IMP were dizziness, feeling of relaxation and numbness of mouth and tongue.

PHARMACOKINETICS

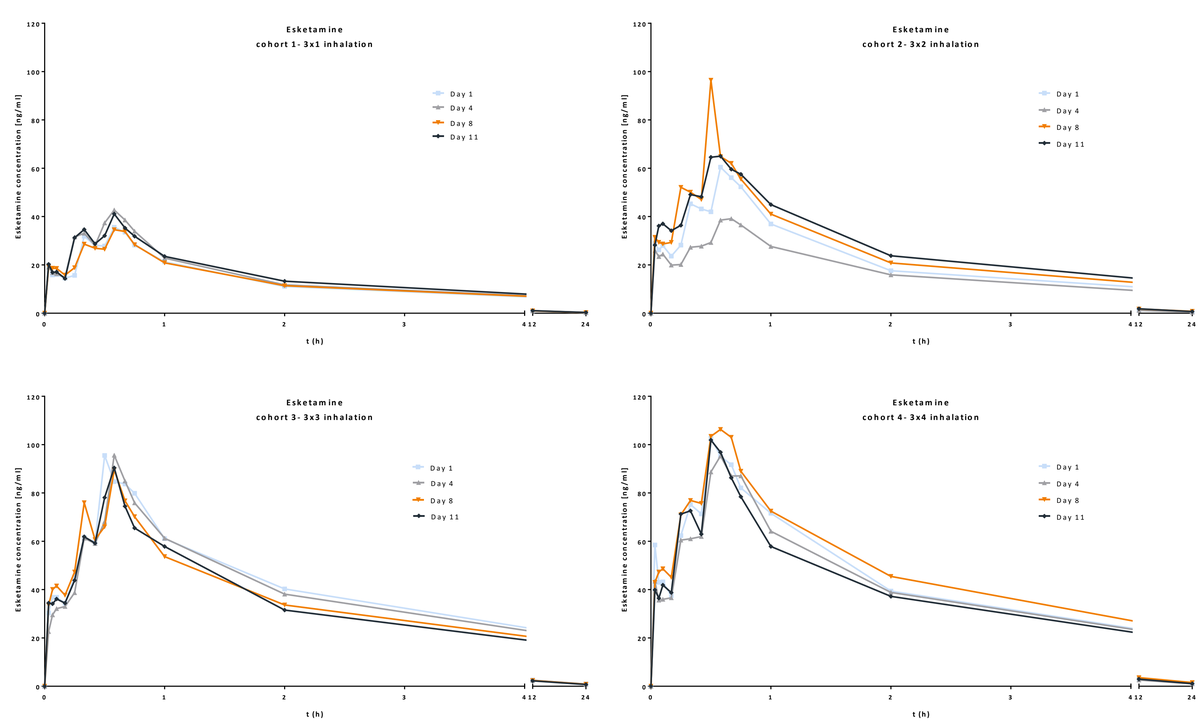

Fig.2. Mean of Esketamine's plasma concentration for all cohorts and all dosing days.

Pharmacokinetic parameters for Esketamine are shown in Tab.5.

Tab.5. Esketamine's pharmacokinetic parameters for all cohorts and all dosing days [mean, (SD)].

Parameter	Cohort	N	Day 1	Day 4	Day 8	Day 11
Cmax [ng/mL]	1	6	39.57 (10.26)	60.88 (27.99)	38.5 (15.24)	47.24 (17.53)
	2	6	62.18 (12.48)	46.91 (13.49)	112.57 (110.44)	82.76 (29.53)
	3	6	115.21 (64.44)	100.27 (26.2)	92.7 (37.14)	106.49 (51.48)
	4	7/5**	109.36 (36.40)	103.351 (23.65)	115.92 (46.79)	110.5 (52.57)
T1/2 [h]	1	6	4.76 (2.03)	5.49 (2.17)	4.42 (2.06)	5.44 (1.88)
	2	6	4.78 (1.16)	6.82 (1.25)	5.25 (1.44)	5.76 (1.36)
	3	6	5.42 (1.74)	5.59 (1.51)	5.48 (1.86)	5.58 (1.51)
	4	7/5**	5.71 (2.11)	5.47 (2.56)	6.96 (2.06)	5.52 (1.95)
AUC(0-24) [ng/mL*h]	1	6	85.61 (27.08)	95.34 (28.31)	87.9 (36.28)	97.68 (29.71)
	2	6	143.98 (27.32)	111.44 (29.2)	168.7 (28.54)	178.79 (28.51)
	3	6	266 (76.56)	253.97 (57.76)	237.3 (78.71)	225.3 (96.18)
	4	7/5**	285.78 (93.81)	260.05 (55.59)	313.32 (111.4)	262.36 (126.94)
AUC(0-inf) [ng/mL*h]	1	6	87.3 (28.98)	97.8 (29.8)	89.55 (38.38)	100.28 (31.56)
	2	6	148.3 (27.86)	116.44 (31.59)	174.5 (28.2)	184.64 (28.12)
	3	6	273.95 (78.21)	261.13 (57.83)	243.99 (79.2)	231.71 (98.14)
	4	7/5**	296.41 (95.84)	271.58 (51.67)	329.91 (120.44)	271.9 (133.64)

** On Days 1 and 4 N=7, on Days 8 and 11 N = 5

The Esketamine Cmax was achieved 30-40 minutes after the start of dosing for all cohorts and all doses.
The Esnorketamine mean Cmax values were 51,9-77,1 % of the Esketamine Cmax mean values for all cohorts and all dosing days.

SUMMARY AND CONCLUSIONS

- Inhaled Esketamine was well tolerated with no serious AEs.
- Most reported adverse events were classified as mild and few were classified as moderate.
- The dose-response relationship between IMP dose and AEs occurence was observed for dizziness, feeling of relaxation nad numbness of mouth and tongue.
- Symptoms reported through questionnaire may suggest possible psychoactive (psychomimetic/dissociative) symptoms after administered doses of Esketamine, in some participants.
- 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 obtained results suggest low intrasubject variability.
- The study results justify further development of inhaled Esketamine in patients suffering from treatment–resistant depression (TRD).

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