

Safety assessment of esketamine administered via dry powder inhalation in animals and humans during preclinical toxicology and phase I clinical study

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Disclosures:

S.J., J.S, J.P. and M.M. are employees of Celon Pharma S.A.. M.M. and M.W. are shareholders of Celon Pharma S.A.. S.J. and M.W. are patent authors.

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INTRODUCTION

Ketamine has been known and used as an anaesthetic for over 50 years. Recently, several clinical studies with both single and multiple administrations have demonstrated a rapid antidepressant effect of ketamine in patients suffering from depression, mostly with treatment-resistant depression (TRD), as well as reduction in suicidal thoughts. However, ketamine undergoes a strong first-pass metabolism effect, excluding the possibility of oral administration. In order to address a reliable and comfortable method of administration, we developed an innovative approach to deliver esketamine by dry powder inhalation. The novel inhalation route could provide a solution for ketamine delivery and may offer additional advantages including efficient and precise dosing and preferable administration over intravenous route. We present here the safety profile of esketamine inhaled as dry powder assessed during preclinical and clinical studies.

MATERIALS AND METHODS

Preclinical

Toxicity studies

14-day toxicity study in rats:

- Wistar rats, 82 animals (41 males and 41 females).
- Test item: esketamine hydrochloride and excipients: lactose monohydrate and magnesium stearate in dry inhalation powder.
- The test and vehicle control items were administered for 120 minutes by inhalation exposure for 28 consecutive days followed by a 14-day recovery period.
- Target dose levels (estimated achieved dose): 0 mg/kg (0), 5 mg/kg (5,7), 15 mg/kg (18,0), 40 mg/kg (36,5).

28-day toxicity study in dogs with cardiovascular assessment:

- Beagle dogs, 40 (20 males, 20 females).
- Test item: esketamine hydrochloride and excipients: lactose monohydrate and magnesium stearate in dry inhalation powder.
- The test and vehicle control items were administered for up to 120 minutes by inhalation exposure for 14 consecutive days with 3 days observation period.
- Target dose levels (estimated achieved dose): 0 mg/kg (0), 4 mg/kg (4,3), 12 mg/kg (13,8), 40 mg/kg (46).

Safety pharmacology

Safety Pharmacology Study of the Central Nervous System:

- Wistar rats, 32 males.
- Assessment by Functional Observational Battery (FOB) on behavioral, neurological and autonomic parameters.
- Solution of esketamine in PBS. Dose levels : 0 mg/kg, 5 mg/kg, 15 mg/kg, 35 mg/kg. Doses were administered at 25% increments, with a ~2 minute observation period between each increment, until the full dose was administered (over ~6 minutes).

Safety Pharmacology Study of the Respiratory System:

- Wistar rats, 32 males.
- Assessment by pletysmographs.
- Solution of esketamine in PBS. Dose levels : 0 mg/kg, 5 mg/kg, 15 mg/kg, 35 mg/kg. Doses were administered at 25% increments, with a ~2 minute observation period between each increment, until the full dose was administered (over ~8 minutes).

The studies were performed by external service provider.

Clinical

Single dose study

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 cohorts (n = 3 / cohort).
- In PART B of the study subjects performed a dosing sequence: 3 inhalation events spread over 30 minutes (3-12 inhalations total). There were 4 cohorts (n = 3 / cohort).

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.

Multiple dose study

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 a 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 total) There were 4 cohorts (n = 8 / cohort) with randomization index 3:1.

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 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, 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.

Safety evaluation

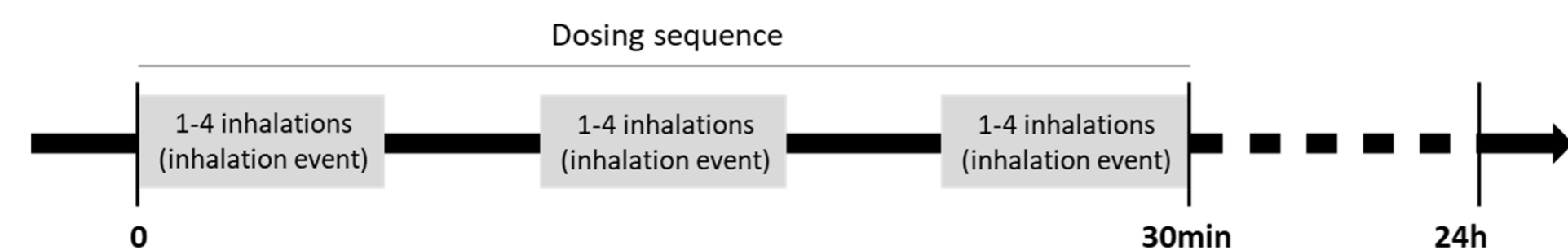
- Safety assessments included: adverse events (AE) reporting, clinical laboratory tests (haematology, blood chemistry, urinalysis), vital signs measurements, physical examination, electrocardiography (ECG).

Questionnaire

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

Statistics

- Adverse events and symptoms reported through subject's questionnaire were evaluated descriptively.



SUMMARY AND CONCLUSIONS

- During preclinical assessment, at all dose levels, several transient and expected clinical observations consistent with the test item's pharmacological activity were observed. None of the observed changes were deemed to be toxicologically significant.
- Inhaled esketamine was well tolerated with no serious adverse events during phase I clinical trial.
- Most of the reported adverse events were classified as mild with only a few classified as moderate.

RESULTS

Preclinical

14-day toxicity study in rats		28-day toxicity study in dogs and cardiovascular assessment		Safety Pharmacology - FOB		Safety Pharmacology - Respiratory	
Dose mg/kg	Side effects	Dose mg/kg	Side effects	Dose mg/kg	Side effects	Dose mg/kg	Side effects
4	No clinical signs.	5	Slight, transient incoordination in one animal; average food consumption in treated male animals was lower (no body mass loss); increase in heart rate by 7.8%.	5	Changes in the animals' posture/activity in their home cage, rearing, gait and body temperature.	5	No significant effects observed.
12	No clinical signs; trend in increase of aspartate aminotransferase values.	15	Salivation (slight to moderate), slight to moderate incoordination, slightly decreased activity, shaking; average food consumption in treated male animals was lower (no body mass loss); increase in heart rate by 39.6%.	15	Changes in the animals' posture/activity in their home cage, rearing, exploratory activity, arousal, gait, flexor reflex and body temperature.	15	Transient increases in tidal volume (37 and 41%, respectively) and minute volume increase (17 and 13% respectively), and decreases in respiratory rate (12% for both dose levels) compared to control values. By 2 hours post dose, the changes were no longer seen.
40	No clinical signs; trends in a number of haematological parameters, including decreasing neutrophils in females, trend in increase of aspartate aminotransferase values.	35	Slight to extreme incoordination, slight to extreme salivation, labored respiration, slight decreased activity, shaking, slight increased respiration; average food consumption in treated male animals was lower (no body mass loss); increase in heart rate by 88.4%; minimal to mild increases in alveolar macrophages of the lungs (present also in vehicle animals) no longer present after recovery period.	35	Changes in the animals' posture/activity in their home cage, rearing, exploratory activity, arousal, gait, motor activity, flexor reflex, pupil response, extensor thrust reflex, pinna reflex, proprioceptive positioning, surface righting reaction, forelimb/hindlimb grip strength and body temperature.	35	

Clinical

SINGLE DOSE IN HEALTHY VOLUNTEERS

AE description	PART A		PART B		
	AE observed (N(%))	Subjects affected (N(%))	AE observed (N(%))	Subjects affected (N(%))	
Abdominal pain	2 (8.3%)	2 (11.1%)	Concentration disorders	3 (8.1%)	2 (16.7%)
Dizziness	7 (29.2%)	7 (38.9%)	Cough	1 (2.7%)	1 (8.3%)
Fainting	1 (4.2%)	1 (5.6%)	Disorders in time perception	1 (2.7%)	1 (8.3%)
Fatigue	2 (8.3%)	2 (11.1%)	Dizziness	9 (24.3%)	7 (58.3%)
Headache	4 (16.7%)	3 (16.7%)	Feeling of a heavy head	3 (8.1%)	1 (8.3%)
Herpes simplex	1 (4.2%)	1 (5.6%)	Feeling of anxiety	1 (2.7%)	1 (8.3%)
Hypertension	4 (16.7%)	4 (22.2%)	Feeling of calmness and relaxation	1 (2.7%)	1 (8.3%)
Sleepiness	1 (4.2%)	1 (5.6%)	Feeling of hot feet	1 (2.7%)	1 (8.3%)
Sweating increased	1 (4.2%)	1 (5.6%)	Feeling of relaxation	9 (24.3%)	4 (33.3%)
Tremor	1 (4.2%)	1 (5.6%)	Feeling of uncertainty	1 (2.7%)	1 (8.3%)
Total	24 (100.0%)	18 (100.0%)	Total	37 (100.0%)	12 (100.0%)

MULTIPLE DOSES IN HEALTHY VOLUNTEERS

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 temp. 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%)*

AE description (questionnaire)	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%)

AE description (questionnaire)	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 „high“	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%)*