ESKETAMINE AND METHODS

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-ketamine. 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-ketamine. 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 present 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 16 consecutive inhalations, called an inhalation event. There were 6 cohorts (n=5/cohorts).

In PART B of the study subjects performed a dosing sequence: 3 inhalations (5-12 inhalations (3)) Fig.1. There were 6 cohorts (n=5/cohorts).

Study population

• 12 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 containing esnorketamine hydrochloride as an active pharmaceutical ingredient, inhalation powder delivered by dry powder inhaler (DPI).

• One inhalation of IMP contained 4.6 mg of esnorketamine hydrochloride (4 mg of esnorketamine free base) and excipients: lactose monohydrate and magnesium stearate.

Pharmacokinetics

• Blood samples for PK analysis, in each part, were collected in time-points: predose (1 h before the IMP administration), 0, 1, 2, 4, 6, 10, 15, 20, 30, 45, 60 and 1, 2, 6, 24 hours after the start of dosing.

• ESKETAMINE and Esnorketamine concentration measurements were performed in human EDTA K2 plasma samples using UPLC/MS/MS racemic methods.

Safety evaluation

• Safety evaluation 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 conducted during both parts of the study.

Statistics

• Descriptive data was analyzed 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). Esnorketamine and ESKETAMINE 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

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

<table>
<thead>
<tr>
<th>Part A</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>18-49</td>
<td>20-49</td>
<td>38</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>50-80</td>
<td>60-80</td>
<td>110</td>
</tr>
<tr>
<td>Body Mass Index (BMI)</td>
<td>20-25</td>
<td>20-25</td>
<td>100</td>
</tr>
</tbody>
</table>

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, a total of 62 adverse events (1 event per subject) were observed. In PART B, a total of 94 adverse events (1 event per subject) were observed.

Table 2. Adverse events observed in PART B of the study.

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe events</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Mild events</td>
<td>2 (9.1%)</td>
<td>1 (5.6%)</td>
<td>3 (6.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>2 (9.1%)</td>
<td>1 (5.6%)</td>
<td>3 (6.3%)</td>
</tr>
</tbody>
</table>

PHARMACOKINETICS

Table 5. Pharmacokinetic parameters from PART A and PART B of the study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PART A</th>
<th>PART B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (h)</td>
<td>1.5 (1.5)</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>T1/2 (h)</td>
<td>5 (3)</td>
<td>7 (3)</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>70 (25)</td>
<td>80 (25)</td>
</tr>
<tr>
<td>AUClast (ng*h/mL)</td>
<td>500 (250)</td>
<td>550 (250)</td>
</tr>
</tbody>
</table>

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.

• 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/disociative) 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).

REFERENCES

