Ketamine has been known and used as an anesthetic 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, as well as treatment-resistant depression (TRD), as well as reduction in social isolation. However, ketamine undergoes a strong first-pass metabolism effect, excluding the possibility of oral administration. In order to address this and develop a more affordable 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 dose and predictable and controllable administration over intravenous route. We present here the safety profile of esketamine inhaled as dry powder administered during preclinical and clinical studies.

### INTRODUCTION

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

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**Disclosures:** S.J., J.S.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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**SUMMARY AND CONCLUSIONS**

- During preclinical assessment, at all dose levels, several transient and precise clinical observations consistent with the test item's pharmacological activity were noted. 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.

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**RESULTS**

**Preclinical**

- **Safety pharmacology:**
  - No significant effects observed.

**Clinical**

- **Multiple doses in healthy volunteers**
  - Dose: 150 mg/kg
  - Number of subjects: 19
  - No significant effects observed.

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**MATERIALS AND METHODS**

**Preclinical**

- **Safety studies**
  - **Safety pharmacology:**
    - **Inhalation toxicology in rats**
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