CLINICAL STUDY REPORT

Bioavailability study of intranasal sufentanil/ketamine fixed combination in healthy volunteers

Protocol no.: PDC 01-0204
EudraCT no.: 2020-004488-14

Investigational Product:	Sufentanil(citrate)/ketamine(hydrochloride) for intranasal use CT001
Development Phase:	**1**
Study Initiation Date:	**17-MAR-2021**
Study Completion Date:	**02-JUN-2021**
Report Completion Date:	**15-SEP-2022**
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Responsible for Sponsor:	Jes Trygved, CEO

GCP STATEMENT
This study was conducted in compliance with Good Clinical Practices, according to the ICH Harmonised Tripartite Guideline.

CONFIDENTIALITY STATEMENT

2 SYNOPSIS

Title of Study:

Bioavailability study of intranasal sufentanil/ketamine fixed combination in healthy volunteers

Co-ordinating/principal Investigator:

Mads U. Werner, Consultant MD, PhD, DMSc

Study Centre(s):

DanTrials, Zelo 1 unit, Bispebjerg Hospital, Bispebjerg Bakke 23, Copenhagen NV

Publication (reference):

Not applicable

Studied Period (years):	**Clinical Phase:**
FSFV: 17 MAR 2021 LSLV: 02 JUN 2021	Phase 1

Objectives:

Primary objective: To investigate the absolute bioavailability of intranasal sufentanil/ketamine in a standardized study set-up with healthy volunteers

Secondary objectives: To assess the pharmacokinetic profile and safety of intranasal administration sufentanil/ketamine

Methodology:

Phase1 study (single site) including a randomized three-treatment, three-period, open-label, single dose, cross-over design in 12 evaluable healthy male volunteers

Number of Participants (total and for each dosage):

Total number of participants were enrolled in the study:15
Total participants dosed with IN sufentanil/ ketamine (CT001): 14
Total participants dosed with IV ketamine: 15
Total participants dosed with IV sufentanil: 14

Twelve participants completed as per protocol.

Diagnosis and Criteria for Inclusion:
In order to be eligible for the study, the participants was to fulfil all of the following criteria:

i) Healthy male volunteers
ii) Age from 18 up to 55 years
iii) Non-smokers
iv) Body mass index (BMI) from 18.5 kg/m^2 up to 30 kg/m^2

v) Categorized as ASA Physical Status Class 1 or 2
vi) Clinically normal medical history, physical findings, vital signs, ECG and laboratory values as judged by the investigator at the time of the screening visit. A potential participant with measurements outside the reference range for the population being studied may be included at the investigator´s discretion provided the finding is unlikely to introduce additional risk factors, jeopardize study integrity, or to interfere with the study assessments or procedures.
vii) The potential participant gives written informed consent for participation in the study

In order to be eligible for the study, the participant was not to fulfil any of the following criteria:

i) Current or history of any clinically significant disease or disorder, which, in the opinion of the investigator, may put the potential participant at risk when participating in the study, or influence the potential participant's ability to participate in the study or influence the study results
ii) Any clinically significant illness, medical/surgical procedure or trauma within 4 weeks of the administration of investigational product that is likely to introduce additional risk factors, jeopardize study integrity, or to interfere with the study assessments or procedures
iii) Mental illness
iv) Opioid Risk Tool score of >3
v) Pain Catastrophizing Scale score, total points >30
vi) Hospital Anxiety and Depression Scale (HADS), points ≥11 for anxiety or ≥11 points for depression
vii) Daily intake of analgesics
viii) History of alcohol or drug abuse or use of illicit drugs. Positive screening for drugs of abuse at the screening visit or on admission to the clinic prior to the administration of investigational product.
ix) Use of prescription drugs within 14 days or over-the-counter drugs 24 hours (intranasal medication 48 hours) prior to the first dose of study medication, unless it is the opinion of the Investigator that the medication will not interfere with the study procedures or compromise participant
x) Planned any scheduled invasive treatment or medical/surgical procedure during the study period
xi) Abnormal nasal cavity/airway such as:
    a. major septal deviation
    b. evidence of previous nasal disease, surgery, and dependence of inhaled drug
    c. current significant nasal congestion due to common cold
    d. Qualitatively decreased air flow in each nasal passage
xii) History or presence of allergy to the study drug or drugs of this class, or a history of drug or other allergy that, in the opinion of the investigator, contraindicates their participation
xiii) Positive tests for HIV, hepatitis B and hepatitis C
xiv) Positive COVID-19 test or clinical symptoms of COVID-19 (testing of participants will follow the health authorities' guidelines and current guidelines for the Capital Region of Denmark)
xv) Is currently participating in or has participated in an interventional clinical trial with an investigational compound or device within 30 days of signing the informed consent for this study
xvi) Blood donation within 4 weeks prior to the first dosing visit

Test Product, Dose, Mode of Administration, Batch No.:

CT001: Sufentanil 90 mcg/ml + ketamine 90 mg/ml, solution for nasal spray, (batch number: 1085441) administered with nasal spray device Aptar CPS pump 0.1 ml per actuation (lot number 25204504) and

U-save 3 ml glass bottle (lot number N103127S). The administered intranasal dose was 27 mcg sufentanil + 27 mg ketamine

Duration of Treatment:

Three-treatment, three-period, single dose cross-over design with a washout period of minimum 5 days and maximum 3 weeks between treatments.

Reference Therapy, Dose, Mode of Administration, Batch No.:

Ketamine Abcur solution for injection, 50 mg/ml (batch number: 207266)
(Intravenous (IV) ketamine 10 mg as a single bolus dose)
and
Sufenta, solution for injection, 5 mcg/ml (batch number: DW2V)
(Intravenous (IV) sufentanil 10 mcg as a single bolus dose)

Criteria for Evaluation:

Efficacy variables

Primary variables:

Pharmacokinetic parameters maximal plasma concentrations (C_{max}), area under the curve representing total drug exposure (AUC(0-t)), determined by the plasma concentration data of analytes

Secondary variables

Pharmacokinetic parameters elimination half-lives ($T_{½}$), clearance (CL), volume of distribution (V), determined by the plasma concentration data of analytes

Safety:

- The number and proportion (%) of participants with AEs and the severity of AEs.
- Physical examination
- Vital signs including blood pressure (systolic and diastolic), heart rate, respiratory rate and blood oxygen level
- Assessment of local tolerance by inspection of the nasal cavity

Statistical Methods:

The non-compartmental pharmacokinetic endpoints $AUC_{0\text{-}tlast}$, terminal half-life ($T_{½}$), $AUC_{0\text{-}\infty}$, C_{max}, Tm_{ax}, CL/F and Vd/F were derived from the concentration time profile from 0 to 24-48 hours post dose for sufentanil and ketamine. All parameters were summarised using mean, SD, geometric mean and median, and the difference of log-transformed values for $AUC_{0\text{-}\infty}$ for intravenous and intranasal administration were used to calculate the absolute bioavailability with back-transformed 95% confidence intervals of the log-difference (corresponding to the ratio on linear scale). Non-linear mixed effect modelling was utilised to generate joint population PK models for intravenous and intranasal administration of the drugs separately (one model for ketamine, one model for sufentanil) allowing the model-dependent estimation of PK parameters including absolute bioavailability. Choice of the number of distribution compartments and absorption model for intranasal administration were driven by the obtained data.
Descriptive statistics were used for all safety parameters.

SUMMARY – CONCLUSIONS

Pharmacokinetic Results:

Non-compartmental analysis allowed the estimation of absolute bioavailability for both ketamine and sufentanil, with minimal extrapolation required in calculation of the AUC extrapolated to infinity. The median and range of estimated bioavailability using extrapolation to infinity was 46.3% [30.4%/95.2%] for ketamine, and 37.5% [25.8%/68.7%] for sufentanil.

Compartmental models allowed the description of ketamine, nor-ketamine, and sufentanil PK with three compartments for the distribution of sufentanil or ketamine and l, an additional two compartments for nor-ketamine, and a combined zero and first order process for the absorption of IN administered ketamine and sufentanil.

Goodness of fit plots indicated that the obtained models provided an adequate description of ketamine, nor-ketamine, and sufentanil concentration time profiles, and visual predictive checks demonstrated that the models can be used for simulation purposes.

The estimated bioavailability for ketamine was 46.8% with a 95% confidence interval of 43.6%/50.1% and an inter-individual variability of 28.6%, matching the values obtained with non-compartmental analysis.

The estimated bioavailability for sufentanil was 39.4% with a 95% confidence interval of 32.8%/46.0% and an inter-individual variability of 20.8%, matching the values obtained with non-compartmental analysis.

Safety Results:

A total of 16 treatment emergent adverse events (TEAEs) were reported in 11 of the randomised participants (73%). Nine of the TEAEs (56%) were deemed related to IMP. Five (31%) of the TEAEs were associated with the sufentanil/ketamine IN, 7 (44%) to the ketamine reference product and 4 (25%) to the sufentanil reference product. No SAEs were reported. The most common TEAEs were headache (Total=5 (31%); sufentanil/ketamine=2 (12%); Ketamine reference product=2 (12%), Sufentanil reference product=1 (6%)), rash (Total=4 (25%); sufentanil/ketamine IN=1 (6%); Ketamine reference product=3 (19%), and epistaxis (Total=2 (12%); sufentanil/ketamine IN=1 (6%); Sufentanil reference product=1 (6%)). All of the TEAEs were of mild severity, meaning that they were transient and easily tolerated.

No clinically significant changes in participants' vital signs (systolic blood pressure, diastolic blood pressure, heart rate, blood oxygen level, respiratory rate) were observed during the study and no interventions were required.

A visual inspection of the nasal cavity performed by a trained investigator with a nasal speculum at the dosing visit involving sufentanil/ketamine (test product) revealed no changes from baseline in the nasal mucosa and no unpleasant symptoms related to nasal administration were recorded.

No participants reported opiate withdrawal symptoms (assed by the Clinical Opiate Withdrawal Scale (COWS)) or psychological adverse drug responses (assessed by the Drug Effect and Drug Liking scale) during the study period.

Conclusion:

The safety profile of the test product was consistent with the two reference products.