

**[REDACTED] pharmacokinetic
modelling of oral and intranasal
formulations of oxycodone in healthy
volunteers**

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Statistical Analysis Plan

(version 1.0, 15th September 2025)

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1. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
BP	Blood Pressure
CNS	Central nervous system
CRS	Clinical Study Report
ECG	Electrocardiogram
EOS	End of Study
HR	Heart Rate
HVD	Half value duration
IM	Intramuscular
IN	Intranasal
IV	Intravenous
LLOQ	Lower Limit of Quantification
MedDRA	Medical Dictionary for Regulatory Activities
N	Number
OR	Oral
PSCA	Potentially Clinically Significant Abnormalities
PBPK	Physiologically Based Pharmacokinetic
SAP	Statistical Analysis Plan
TEAE	Treatment-Emergent Adverse Event
URC	Clinical Research Unit

2. VERSIONS AND INVESTIGATOR

2.1. Version

Version	Date	Comments
1.0	15 th September 2025	-

2.2. Investigators

Principal Investigators	<div><div>[Redacted]</div><div>[Redacted]</div><div>[Redacted]</div><div>[Redacted]</div><div>[Redacted]</div><div>[Redacted]</div><div>[Redacted]</div></div>
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1. INTRODUCTION

This Statistical Analysis Plan (SAP) describes in detail the statistical methodology applied for the analysis of pharmacokinetic (PK), pharmacodynamic (PD), and safety data in the Phase I crossover study:

“**██████████ pharmacokinetic modelling of oral and intranasal formulations of oxycodone in healthy volunteers.**”

This SAP is aligned with the approved protocol and reflects the analyses conducted in the Clinical Study Report (CSR).

2. BACKGROUND INFORMATION

Oxycodone is a semisynthetic opioid used in the management of moderate to severe pain.

Oxycodone's mechanism of action appears to work through stimulating the opioid receptors found in the central nervous system that activate responses ranging from analgesia to respiratory depression to euphoria.

Oxycodone's hepatic metabolism is extensive and completed by 4 main reactions. CYP3A4 and 3A5 regulate N-demethylation to noroxycodone, CYP2D6 regulates O-demethylation to oxymorphone (an active metabolite, deemed undetectable in many instances) and noroxymorphone (from noroxycodone), less characterized enzymes regulate 6-ketoreduction, and unknown enzymes perform conjugation. Oxycodone and its metabolites are eliminated in the urine. The apparent elimination half-life of oxycodone PO is 3.2 hours for immediate release formulations and 4.5 hours for extended release formulations. Noroxycodone has a half-life of 5.8 hours, oxymorphone has a half-life of 8.8 hours, noroxymorphone has a half-life of 9 hours.

For OxyNorm 10 mg/ml in oral solution, the mean oral bioavailability is 87%. The estimated half-life of oral oxycodone is 4.5 hours and the peak concentrations are achieved at 1 hour. A solution for injection was administered intranasally by Takala et al (1997). The estimated half-life of intranasal oxycodone was 2.5 hours and the peak concentration after the intranasal administration was achieved at 25 min (95% CI: 20-250 min). The mean bioavailability of intranasal administration was 46% (95% CI 25%-67%; min-max: 16%-90%).

Regarding pharmacodynamics, Oxycodone acts directly on a number of tissues not related to its analgesic effect. These tissues include the respiratory center in the brain stem, the cough center in the medulla, muscles of the pupils, gastrointestinal tract, cardiovascular system, endocrine system, and immune system. Oxycodone's effect on the respiratory center is dose dependent respiratory depression. The action on the cough center is suppression of the cough reflex. Pupils become myopic or decrease in size, peristalsis of the gastrointestinal tract slows, and muscle tone in the colon may increase causing constipation. In the cardiovascular system histamine may be released leading to pruritis, red eyes, flushing, sweating, and decreased blood pressure. Endocrine effects may include increased prolactin, decreased cortisol, and decreased testosterone secretion. It is not yet known if the effects of opioids on the immune system are clinically significant.

Very common adverse events are somnolence, dizziness, headache, constipation, nausea, vomiting and itching. Common adverse events are anxiety, confusion, depression, insomnia, restlessness, abnormal flow of thought, tremors, dyspnea, bronchospasm (especially in asthmatic patients), abdominal pain, diarrhea, dry mouth, dyspepsia, rash, ample sweating, faintness.

Large doses of oxycodone could depress the respiratory center considerably and circulation to a lesser extent. Overdose may lead to complete respiratory depression (apnea), bradycardia, hypotonia, miosis, hypotension, somnolence, which may lead to coma or intense grogginess, and death.

Some instructions will be followed for the administration:

- Oral oxycodone: In the absence of a significant bioavailability difference between oral and Intranasal administration of oxycodone solution, it is proposed to administer oxycodone orally (oral solution) 0.1 mg/kg, in the range of 5-9 mg.
- Intranasal administration of oxycodone solution: 0.1 mg/kg (subjects weighing approximately 70 kg, the total volume of the oxycodone chloride solution which will be sprayed intranasally will be 0.70 mL in total) with a total dose of 7 mg. The volume of one spray will be 0.1 mL. The nurse will administer the spray alternately in both nostrils while the subject is in a supine position to minimize dripping. If the subject begins coughing, sneezing or reports needing to swallow the solution, we will wait 2–3 minutes before proceeding with another sequence of applications. The Intranasal doses will be administered over a period of 5 minutes. Subjects will be trained in intranasal administration prior to receiving the drug products. Doses in oral or intranasal administration will follow rounding down rule for body weight-based dosing.

The OXY-1 study was designed as a Phase I clinical trial to characterize the PK and PD of oxycodone (intranasal and oral) in healthy subjects, which will be used to verify/validate nasal-CNS-PBPK (Physiologically Based Pharmacokinetic) model predictions following intranasal dosing.

3. STUDY DESIGN

A single-dose, 2-period, 2-sequence, fasting, open label, crossover randomized design, comparing the pharmacokinetics (PK) and pharmacodynamics (PD) of intranasal and oral oxycodone solutions.

3.1. Study drugs

Oral solution of oxycodone (OXYNORM CONCENTRADO 10 mg/ml). Oxycodone (OXYNORM 10 mg/mL solution for IV/perfusion) administered intranasally with Nasal delivery system of Aluneb (<https://aluneb.cinfa.com/>) or similar.

3.2. Number of subjects

Eight volunteers were planned to be included in the trial. Eight volunteers completed the trial and were included in the statistical analysis.

4. OBJECTIVES

4.1. General objective

To characterize the PK and PD of two formulations of oxycodone (OR and IN) in healthy subjects, which will be used to verify/validate nasal- central nervous system (CNS)-PBPK model predictions following IN dosing.

4.2. Specific objectives

4.2.1. Pharmacokinetics objectives

To calculate plasma PK parameters listed below using a non-compartmental model:

- Observed maximum concentration: C_{max} .
- Observed last concentration: C_{last} .
- Time to observed maximum concentration: T_{max} .
- Time lag (time to first measurable plasma concentration): t_{lag} .
- Area under the concentration-time curve (AUC_{0-24h} , AUC_{0-t} , $AUC_{0-\infty}$) where t is the latest observed timepoint.
- Terminal elimination half-life: $t_{1/2}$.
- Apparent clearance: Cl/F .
- Apparent volume of distribution: Vd/F .
- Elimination rate constant (λ_z).

4.2.2. Safety objectives

To evaluate drug safety focusing on:

- Treatment-Emergent Adverse Event (TEAEs) from Day 1 to End of Study (EOS).
- Potentially Clinically Significant Abnormalities (PSCAs) in vital signs, Electrocardiogram (ECG) and safety laboratory parameters from Day 1 to EOS.

4.2.3. Pharmacodynamic objectives

To assess the effects of oxycodone on Pupil size.

5. Analysis Population

5.1. Intent-to-Treat population

The ITT population will include all randomized subjects who receive at least one dose of study drug and have at least one post-baseline evaluation.

5.2. Pharmacokinetic population

The PK population will include all randomized treated subjects with evaluable PK data sufficient to allow reliable estimation of primary PK parameters using non-compartmental analysis.

Subjects with major protocol deviations that could meaningfully affect PK interpretation may be excluded from the PK population.

5.3. Pharmacodynamic population

The PD population will include all randomized treated subjects with evaluable PD data, defined as at least one valid post-baseline pupil size assessment within a treatment period. This is consistent with the protocol definition of the PD analysis set.

5.4. Safety population

The Safety population will include all randomized subjects who receive at least one dose of study drug by either route. Safety analyses will be performed according to the actual treatment received in each period.

6. General Statistical Principles

All statistical analyses will be performed using validated statistical software such as R or SAS. Pk parameters will be derived using validated non-compartmental analysis software (Phoenix™ WinNonlin).

Given the exploratory nature of this Phase I study and the limited sample size, the analyses will be primarily descriptive. Continuous variables will be summarized by treatment and timepoint, as applicable, using:

- N
- Mean
- SD
- SEM
- Median
- Minimum
- Maximum
- 95% confidence interval, where appropriate.

Categorical variables will be summarized using counts and percentages.

No formal sample size calculation based on statistical power was used. No interim analysis is planned. Missing data will generally not be imputed, and analyses will be based on observed data only.

Where inferential analyses are performed for repeated quantitative variables, linear mixed effects models may be used, including fixed effects for treatment, time, period, sequence, and treatment-by-time interaction when appropriate, with subject as a random effect. These analyses will be considered exploratory. A nominal two-sided alpha level of 0.05 may be used for exploratory purposes only, with no adjustment for multiplicity.

7. DATA HANDLING

No imputation strategy is specified. Due to the short duration of the study and the monitoring performed, the risk of missing data is very low; analyses will be based on observed data.

8. PHARMACOKINETIC ANALYSIS

PK analyses will be performed separately for IN and OR administration of oxycodone using non-compartmental methods. Plasma concentration–time data will be used to derive standard PK parameters, including C_{\max} , t_{\max} , C_{last} , t_{lag} , AUC_{0-t} , $AUC_{0-\infty}$, terminal elimination rate constant (λ_z), terminal half-life ($t_{1/2}$), apparent clearance (CL/F), and apparent volume of distribution (Vd/F).

PK parameters will be calculated using validated non-compartmental analysis software (e.g., Phoenix WinNonlin). AUC will be estimated using the linear trapezoidal rule and λ_z will be determined from the log-linear terminal phase of the concentration–time curve.

All PK parameters will be summarized descriptively by route of administration using standard descriptive statistics (N, mean, SD, SEM, median, minimum, and maximum). Plasma concentration–time profiles will also be presented numerically and graphically using linear and semi-logarithmic plots.

9. PHARMACODYNAMIC ANALYSIS

The PD assessment in this study focuses on changes in pupil diameter following administration of oxycodone. Pupil size will be measured repeatedly throughout each treatment period using a standardized pupillometry device.

For each scheduled timepoint, descriptive statistics will be calculated for observed pupil diameter and for change-from-baseline values. These summaries will include the number of observations, mean, standard deviation, median, minimum, and maximum values.

Time-course profiles of pupil diameters will be graphically presented to illustrate the temporal PD response following IN and OR administration. Separate plots may be generated for observed values and change-from-baseline values. Error bars representing standard deviation or standard error may be included where appropriate.

10. SAFETY ANALYSIS

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Treatment-emergent adverse events (TEAEs) will be summarized by system organ class and preferred term. Additional summaries will include severity, relationship to study drug, and treatment period.

Serious adverse events will be described individually, including detailed narrative summaries when applicable. Listings of all reported adverse events will also be provided.

Vital signs, ECG parameters, and clinical laboratory variables will be summarized descriptively at baseline and at relevant post-dose timepoints. Change-from-baseline values will be presented where appropriate. Potentially clinically significant abnormalities will be identified based on predefined clinical criteria or investigator assessment and will be listed separately.

11. DATA PRESENTATION

Statistical results will be presented in tables, figures, and listings as appropriate. Planned outputs include summaries of subject disposition, protocol deviations, demographic characteristics, pharmacokinetic parameters, pharmacodynamic variables, and safety outcomes.

PK results will include concentration–time tables and graphical representations of mean concentration–time profiles. PD results will include time-course plots of pupil diameter. Safety outputs will include summaries of AEs, laboratory values, vital signs, and ECG parameters.

Individual subject listings may be provided to allow detailed review of the collected data and to support interpretation of summary results.

12.DESVIATION FROM THE SAP

Any deviation from the methods described in this SAP will be documented, justified, and reported in the Clinical Study Report.