

Statistical Analysis Plan

Protocol No. QEV-817-101, 23 September 2025

A Phase 1, Randomized, Open Label, Crossover Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of QEV-817 Oral Suspension in Healthy Volunteers

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Glossary and Abbreviations

Abbreviation	Term
ADaM	Analysis Data Model
ADLB	Analysis dataset for safety laboratory data
ADPC	Analysis dataset for plasma concentration data
ADPP	Analysis dataset for pharmacokinetic parameter data
AE(s)	Adverse Event(s)
AESI	Adverse Events of Special Interest
ATC	Anatomical Therapeutic Chemical
AUC	Area under the plasma concentration vs time curve
AUC _{0-∞}	Area under the plasma concentration-time curve from time zero extrapolated to infinity
AUC _{0-t}	Area under the plasma concentration-time curve from time zero to time t (time of last quantifiable plasma concentration)
BMI	Body mass index
BQL or BLQ	Below the lower limit of quantification
CI(s)	Confidence interval(s)
CL/F	Apparent clearance
C _{max}	Maximum observed plasma concentration
cm	Centimeter
CTCAE	Common Terminology Criteria for Adverse Events
CRU	Clinical Research Unit
CV %	Coefficient of variation (%)
DBP	Diastolic blood pressure
DOX	Doxapram hydrochloride
eCRF	Electronic Case Report Form
ECG	Electrocardiogram
EOS	End of Study
ET	Early Termination
FDA	Federal Drug Administration
GMR	Geometric Mean Ratio
h or hr	Hour(s)
HEENT	Head, ears, eyes, nose, and throat
HPMC	Hydroxypropyl methylcellulose
HIV	Human immunodeficiency virus
HYC	Hydrocodone bitartrate

Abbreviation	Term
ICF	Informed Consent Form
ICH	International Council for Harmonization
IP	Investigational Product
k_{el}	Terminal elimination rate constant
kg	Kilogram(s)
MDE	Minimum Detectable Effect
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
Max	Maximum
m ²	Meter squared
n or N	Number of participants
NCA	Noncompartmental analysis
PD(s)	Pharmacodynamic(s)
PE	Physical examination
PK(s)	Pharmacokinetic(s)
PR	Pulse Rate
PT	Preferred Term
RASS	Richmond Agitation Sedation Scale
RR	Respiratory Rate
SAS	Statistical Analysis Software
SD	Standard deviation
SDTM	Study Data Tabulation Model
SAE(s)	Serious Adverse Event (s)
SAP	Statistical Analysis Plan
SBP	Systolic blood pressure
SEM	Standard Error of the Mean
SoA	Schedule of assessments
SOC	System Organ Class
T	Oral Temperature
TEAE(s)	Treatment emergent adverse event(s)
TESAE	Treatment-emergent serious adverse event
THC	Tetrahydrocannabinol
TLFs	Tables, Listings, and Figures
T _{max}	Time to maximum observed plasma concentration

Abbreviation	Term
$t_{1/2}$	Terminal elimination half-life
V_d/F	Apparent volume of distribution
WHO	World Health Organization

1 Introduction

This is a single center, 2 period, 2-way crossover, open label, randomized, Phase 1 study. The objective of this study is to evaluate the safety, tolerability, and pharmacokinetics (PK) of a single 10 mg therapeutic dose of hydrocodone bitartrate (HYC) with and without a single oral dose of doxapram hydrochloride (DOX) in healthy volunteers who are naltrexone-blocked.

The investigational drug, QEV-817 (HYC+DOX) is an oral suspension that contains a single oral dose of DOX co-administered with a single oral dose of HYC. The reference drug is the same oral suspension containing HYC only.

The safety measurements (laboratory analyses (chemistry, hematology, and urinalysis)) will be provided by BioReference Laboratories. (The safety laboratory results will include SDTM.LB and ADLB datasets.)

-----[REDACTED]----- will provide plasma concentrations for HYC, HYC metabolite, DOX and DOX metabolite. (The plasma concentration data will be included in SDTM.PC and ADPC. The PK parameters will be included in SDTM.PP and ADPP datasets. These datasets are standard according to CDISC for submission.)

This Statistical Analysis Plan (SAP) covers the detailed procedures for performing the Safety and PK statistical analyses and for producing the Tables, Listings, and Figures (TLFs) in the study. The templates in TLF Shells are followed once the SAP is signed and only minor changes to TLFs will occur once the SAP is final (this includes footnotes due to data issues).

Relevant ICH and FDA guidance for statistical approaches will be followed.

The electronic case report form (eCRF) and external data files (PK concentrations from [REDACTED] and PK parameters from Frontage Clinical Services) will be included in the SDTM and ADaM datasets and these will be used to create the Tables, Listings and Figures (TLFs) as specified in the TLF Shells document.

2 Study Objectives

2.1 Primary Objective

- To assess the safety and tolerability of a single oral dose of doxapram hydrochloride (DOX) co-administered with an oral dose of hydrocodone bitartrate (HYC).

2.2 Secondary Objective

- To assess the pharmacokinetic characteristics of both drugs when co-administered orally.

- To evaluate the relative bioavailability of 10 mg oral Hydrocodone bitartrate alone (HYC) to 10 mg oral Hydrocodone bitartrate co-administered with 50 mg oral Doxapram hydrochloride (HYC+DOX) in healthy volunteers.

2.3 Exploratory Objective

- To explore responses on the Richmond Agitation Sedation Scale (RASS).

3 Study Endpoints

3.1 Primary Endpoints:

- Nature, severity, and incidence of AEs.
- Change from baseline in physical examination, vital signs, 12-lead ECG assessment, pulse oximetry, and clinical laboratory tests.

3.2 Secondary Endpoints:

- Plasma PK parameters including (but not limited to): C_{max} , T_{max} , $AUC_{0-\infty}$, AUC_{0-t} , V_d/F , CL/F , and $t_{1/2}$ of DOX and its active metabolite 2-keto- doxapram.
- Plasma PK parameters including (but not limited to): C_{max} , T_{max} , $AUC_{0-\infty}$, AUC_{0-t} , V_d/F , V_{ss}/F , CL/F , and $t_{1/2}$ of HYC and its active metabolite hydromorphone.
- Relative bioavailability comparison of 10 mg oral Hydrocodone bitartrate alone (HYC) to 10 mg oral Hydrocodone bitartrate co-administered with 50 mg oral Doxapram hydrochloride (HYC+DOX) based on maximal plasma concentration (C_{max}), the area under the plasma concentration time curves extrapolated to infinity ($AUC_{0-\infty}$) and AUC to time of last measurable concentration (AUC_{0-t}).

3.3 Exploratory Endpoint:

- RASS score as assessed by physician.

4 Study Design and Methods

This is a single center, 2 period, 2-way crossover, open label, randomized, Phase 1 study to assess the plasma pharmacokinetics of HYC with and without oral DOX and to assess the tolerability of 50 mg oral DOX in combination with 10 mg HYC (QEV-817). The study will be conducted in eight (8) healthy volunteers of both sexes. Up to an additional five (5) subjects may be enrolled as alternates to replace dropouts.

The study consists of a 28-day Screening Period, a four-day treatment period, and a one-day safety follow-up period.

Following confirmation of eligibility, subjects will be randomized (1:1) to one of two crossover treatment sequences as follows:

Sequence Number	Treatment Day 2	Treatment Day 4
Sequence A	HYC	HYC+DOX (QEV-817)
Sequence B	HYC+DOX (QEV-817)	HYC

Abbreviations: DOX = doxapram hydrochloride; HYC = hydrocodone bitartrate

Eligible subjects will receive either a fixed single therapeutic 10 mg oral dose of HYC alone (HYC) or in combination with a fixed single 50 mg oral dose of DOX (HYC+DOX). Treatment Day 2 will be separated by a washout period of 2 days prior to subjects crossing over to Treatment Day 4. Prior to treatment with HYC or HYC+DOX, all subjects will receive naltrexone (opioid antagonist) on Day 1 and Day 3 to block opioid effects (i.e., naltrexone block).

Safety procedures and assessments will be performed according to the Schedule of Assessments (SoA) ([Table 1](#)).

Table 1: Schedule of Assessments

Study Stage/Period	Screening	Treatment				Follow-up
	Day -28 to -1	Day 1	Day 2	Day 3	Day 4	Discharge
Study Day						Day 5/ET
Informed consent ^a	X					
Eligibility	X	X				
Medical history/demographics ^b	X	X				
Previous and concomitant medications			X		X	X
Pregnancy test ^c	X	X				
Chemistry/hematology/urinalysis ^d	X			X		X
Admission/confinement/discharge ^e		X	X	X	X	X
Physical examination ^f	X					
Body weight, height, & BMI calculation	X					
Urine drug and breath alcohol screen ^g	X	X	-		-	
12-lead ECG ^h	X		X		X	X
Vital signs ⁱ			X		X	X
Body temperature ^j			X		X	X
Randomization ^k			X			
Vascular access ^l			X		X	
Premedication ^m		X	X	X	X	
Study drug administration ⁿ			X		X	
Blood sampling for PK ^o			X	X	X	X
Richmond Agitation Sedation Scale (RASS) ^p			X		X	
Adverse event monitoring ^q		X	X	X	X	X

Abbreviations: BMI = body mass index; CRU = Clinical Research Unit; ECG = electrocardiogram; ET = early termination; IV = intravenous; PD = pharmacodynamic(s); PK = pharmacokinetic(s); VAS = visual analog scale; WOCBP = women of childbearing potential.

- a. **Informed consent:** refer to Appendix 1, Section 10.1.3 in the protocol.
- b. **Medical history/demographics:** refer to Section 8.1.1 in the protocol.
- c. **Pregnancy test:** serum pregnancy test will be obtained within one week prior to Day 1 in all female subjects. Urine pregnancy test will be obtained upon admission to the CRU on Day 1 in all female subjects.
- d. **Chemistry/Hematology/Urinalysis:** clinical laboratory tests (serum chemistry, hematology, urinalysis) will be conducted during screening, and 24 hours (± 1 hour) after each study drug administration (i.e., on study Day 3 and prior to discharge on study Day 5). Refer to Section 8.2.2 in the protocol.
- e. **Admission/confinement/discharge:** subjects will be admitted on Day 1 with discharge on Day 5 (not less than 24 hours post last dose) after completion of the safety, PK, and PD assessments. Subjects may be required to remain in the CRU longer at the discretion of the Investigator.
- f. **Physical examination:** includes assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities. A targeted physical may be performed as needed during the study to assess any adverse events. Refer to Section 8.1.2 in the protocol.
- g. **Urine drug and breath alcohol screen:** A urine sample for drug testing and a breath alcohol test will be obtained during screening, and on Day 1 (prior to oral naltrexone treatment). The list of analytes to be tested is provided in Section 10.2. A positive urine drug or breath alcohol test at screening is exclusionary (Section 5.2 in the protocol), except for tetrahydrocannabinol (THC) or cannabinoid metabolites. Refer to Section 8.1.3 in the protocol.
- h. **12-lead ECG:** a 12 lead ECG (recorded after the subject has been resting for at least 5 minutes in a supine or semi-recumbent position) will be collected at screening, after PO naltrexone, but not more than 30 minutes prior to study drug administration on Days 2 and 4; 0.5-, 1-, 2-, 3-, and 4-hours post-dose (± 10 minutes) on Days 2 and 4; and on Day 5 prior to discharge. Refer to Section 8.2.3 in the protocol.
- i. **Vital signs:** include systolic and diastolic blood pressure, pulse rate, respiratory rate, and blood oxygen saturation (pulse oximetry). Vital signs will be assessed at Screening; after PO naltrexone, but not more than 30 minutes prior to study drug administration on Days 2 and 4; 0.5, 1, 2, 3, 4, 12 hours post-dose (± 15 minutes); and on Day 5 approximately 24 hours post Day 4 dose (i.e., prior to discharge). Subjects will remain semi-recumbent for at least 5 minutes prior to blood pressure measurements. Blood pressure measurements will be measured on the same arm throughout the study, whenever feasible. Refer to Section 8.2.4 in the protocol.
- j. **Body temperature:** will be assessed orally at Screening; on Days 2 and 4 pre-dose, 0.5, 1, 2, 3, 4, 12 hours post-dose; and on Day 5 approximately 24 hours post Day 4 dose (i.e., prior to discharge). Refer to Section 8.2.5 in the protocol.
- k. **Randomization:** subjects will be randomized to one of two treatment sequences prior to first study drug administration on Day 2, but after pre-dose assessments. The randomization number will be assigned according to a randomization code list generated by the study site.
- l. **Vascular access:** a peripheral venous catheter will be established for repeated blood sampling during on-site screening and before intake of the study drug on Days 2 and 4. The catheters will be removed after the final blood sample on Days 3 and 5.
- m. **Premedication:** subjects (and possibly including alternate subjects) will receive oral naltrexone HCl (50 mg) prior to study drug administration, as follows:

- Days 1 and 3: 12 ± 1 hours prior to Day 2 and Day 4 study drug administrations.
 - Days 2 and 4: 60 ± 15 minutes prior to study drug administration.
- n. **Study drug administration:** Refer to Section 4.1.1 and 6.1 in the protocol Time of dosing is defined as the start of dose administration.
- o. **Blood sampling for PK:** blood samples for the analysis of HYC, DOX, and metabolites (hydromorphone and 2-keto-doxapram, respectively) in plasma will be collected using a peripherally inserted venous catheter as follows (Section 8.1.4) in the protocol:
- Days 2 and 4: after PO naltrexone, but not more than 30 minutes prior to study drug administration 0.25-, 0.5-, 1-, 1.5-, 2-, 3-, 4-, 6-, 8-, and 12-hour post-dose (± 5 minutes for 0.25 to 4 hours; ± 15 min for 6 to 12 hours);
 - Days 3 and 5: approximately 24 hours after study drug administration (± 30 minutes) on Days 2 and 4 dose, respectively.
- p. **Richmond Agitation Sedation Scale (RASS):** physician assessments on Days 2 and 4 after PO naltrexone, but not more than 30 minutes prior to study drug administration; and 0.75-, 1.5-, 2.5-, 3.5-, 4.5-, 8-, and 12-hours post-dose (± 10 minutes). Refer to Section 8.1.5 in the protocol.
- q. **Adverse events:** will be monitored from the time of admission to the CRU through discharge from the CRU on Day 5. All study- or treatment-related serious adverse events will be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. Refer to Section 8.3 in the protocol.

4.1 Study Assessments

4.1.1 Pharmacokinetic Assessments

The primary PK assessments are the plasma HYC, DOX and their metabolites (hydromorphone and 2-keto-doxapram) concentrations. For the plasma sampling time points and allowable windows for sample collection, refer to [Table 1](#). Blood sample collection that occurs outside of the pre-defined time allowance window will not be considered as a protocol deviation if actual time of collection is recorded. The actual time will be used for final PK analyses.

When the PK blood sample collection coincides with safety assessments or collection of vital signs, ECGs, or other assessments, PK blood samples should be collected as close to the scheduled time point as possible, but other assessments should be performed before the PK blood samples are collected.

4.1.2 Safety Assessments

Safety assessments include the incidence of treatment emergent events (TEAE); study completion and discontinuation information; vital signs; height, weight, and body mass index (BMI), and physical examination (PE); clinical laboratory values, and 12-lead ECG findings.

Adverse events reporting and medical observations will be recorded by the clinic staff throughout the study. Any safety assessment may be repeated at the discretion of the Investigator.

Additional safety parameters may be added at the discretion of the Investigator based on the observations from clinical findings in any subject treated in this study. Safety assessments will be conducted as shown in the SoA ([Table 1](#)).

The Investigator will determine whether any safety related observations are clinically significant or not clinically significant. (Refer to the protocol for further information.)

4.2 Randomization

This is an open label study with regard to treatment (HYC or HYC +DOX). Eligible subjects will be randomly assigned to one of two treatment sequences.

Each subject who signs an informed consent form (ICF) upon Screening will be assigned a unique subject identification (ID) number. The subject ID which will remain unchanged throughout the study. In case of screening failure, the subject ID will not be reused.

If eligible for entry into the study, each subject will be assigned a randomization number and will receive the study treatment assigned to the corresponding randomization number. The randomization number will be generated programmatically by the statistician and are pre-assigned on Day 1 based on the order of arrival at the clinic for admission to the study. The following personnel will have access to the randomization scheme: statistician who provides the randomization scheme, pharmacy personnel preparing investigational product on site, and Bioanalytical personnel analyzing the PK samples. The randomization scheme will be kept in a secure location until the end of the study.

Subjects who are unable to complete the sequence may be replaced and up to 5 additional subjects may be included at the discretion of the Sponsor. Replacement subjects will not be randomized but will be assigned to the same study treatment sequence of the subject being replaced. The replacement subject will be assigned a new Identification Number per standard operating procedure (same random number + 100).

4.3 Sample Size Justification

A sample size of eight (8) subjects was determined by Quivive using statistical analysis of the minimum detectable effect (MDE) from a previous clinical PK interaction for HYC. The sample size determination was based on the plasma PK of oral HYC in human subjects using natural log transformed values of the three (3) primary PK parameters: C_{max} , $AUC_{(0-t)}$, and $AUC_{0-\infty}$. The PK parameter C_{max} was found to have the highest variability of the three (3) primary PK parameters and thus presents a worst-case scenario for the MDE. Based on a power of 0.8 and an α level of 0.05, a one-tailed analysis resulted in a geometric mean ratio (GMR) of 149% for the MDE for the natural log C_{max} , i.e., a minimum increase in C_{max} of essentially 50% may be statistically detected using eight (8) subjects.

4.4 Data Handling

Data listings will be provided for safety, PK and pharmacodynamic (PD) data and parameters by subject. Summary statistics will be provided for safety data, PD, and PK data and parameters by treatment.

For continuous variables, descriptive statistics will include number of subjects (n), mean (arithmetic and geometric), standard deviation (SD, arithmetic and geometric), minimum (min), median, and maximum (max), coefficient of variation (CV, arithmetic, and geometric). For categorical variables, descriptive statistics will include subject counts and percentage of subjects.

Conventions for the presentation of numerical data on safety outputs are as follows:

- Minimum and maximum values will be presented to the same number of decimal places as (eCRF) data.
- Means and medians will be presented to one more decimal place than the eCRF data. Standard deviations will be presented to two more decimal places than the eCRF data.

Plasma concentrations and PK parameters in tables and listings will be displayed with 3 significant figures as follows:

- Values ≥ 0.0001 and < 1 will be reported with 3 significant figures (e.g., 0.0123).
- Values ≥ 1 and < 10 will be reported with 3 significant figures (e.g., 1.02).
- Values ≥ 10 and < 100 will be reported with 3 significant figures (e.g., 10.2).
- Values ≥ 100 and < 1000 will be reported with 3 significant figures (e.g., 102).
- Values ≥ 1000 will be reported with 3 significant figures (e.g., 1020).
- Values = 0 will be reported as 0.
- Values for $T_{\max}$ will be reported using one decimal place (2 significant figures).

For Safety Endpoints:

Baseline is defined as the last value measured prior to the first dose of study drug. For safety parameters that are measured during each study period, the baseline is defined as the value prior to the first dose of the first period. If there is only one baseline collected, then this will be used as the baseline for any of the two study periods.

Change from Baseline is defined as [Post-baseline Value – Baseline Value].

Continuing events (e.g., AEs, concomitant medications) will be summarized using the data cut-off date as the date of completion, with a flag to indicate within listings that the event is continuing.

5 Data Analysis

5.1 Analysis Populations

The analysis populations will be used to summarize the results from this study for enrolled (signed informed consent form (ICF)) and randomized subjects.

Safety Population: All subjects who received at least one dose of study drug. This is the primary population for exposure and safety analyses.

Pharmacokinetic (PK) Population: All subjects in the Safety Population with sufficient concentration data to define at least one HYC, DOX, or metabolite PK parameter. Subjects may be excluded on an individual basis, upon review of all records that have the potential to affect the PK data (e.g., dosing records, AEs, blood sampling records). All such subjects

will be evaluated for PK unless major protocol deviations may have affected the data or if key dosing information is missing. This is the primary population for PK analysis.

In addition, any subject with pre-dose concentrations of QEV-817 (HYC+ DOX) or HYC alone will be presented in the individual plasma concentration and PK listings but excluded from summary plasma concentrations, and PK summary table descriptive statistics if the pre-dose concentration is greater than 5% of the C_{max} value for that subject of that same period. Data from subjects prematurely ending participation in the study may be excluded from the PK analysis.

The frequency and percentage of subjects in each population will be summarized. The listing will include all subjects.

Pharmacodynamic (PD) Population: All randomized subjects who received study drug and have evaluable PD data. This is the primary population for PD analysis.

5.2 Study Subjects

All safety summary tables will be presented as specified in the sections outlined below. All safety listings will include all subject data.

Disposition

Subject disposition will be summarized by treatment sequence for all subjects who signed the ICF and will include the number of subjects who received study treatment and the number and percentage of subjects who completed or prematurely discontinued the study, classified by reasons for premature discontinuation.

Protocol Deviations

Protocol deviations will be identified with reasons for deviation and date of occurrence prior to database lock and may include but are not limited to: inclusion/exclusion violation; use of restricted medication; or not following clinical trial protocol procedures (includes: assessment not performed per protocol; assessment performed outside window, missed assessment, missed visit, PK draw not performed, PK draw performed outside window) that may affect evaluation of PK profile. Protocol deviations will be listed by subject, treatment, and treatment sequence.

5.3 Subject Demographics/Other Baseline Characteristics

Demographic and baseline characteristics will be summarized by treatment sequence and overall (across sequences) for all subjects in the safety population. The demographic and baseline characteristics will consist of age, sex, body mass index (BMI) (kg/m^2), ethnic origin (also referred to as self-reported race and ethnicity in some regions), height (cm), and weight (kg).

Individual demographic and baseline characteristics for the safety population will be listed by subject and treatment sequence.

Age is a calculated parameter. Age will be calculated using the subject's date of birth (date of birth is not included in the database) and the subject's informed consent date.

Continuous variables (age, height, weight, BMI) will be summarized by n, mean, SD, min, median, and max. Number of subjects and percentages will be used to describe categorical (discrete) variables (gender, race, and ethnicity).

5.4 General Medical/Surgical History and Procedures/Non-Drug Therapies

Any current medical conditions and/or other significant medical/surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v28.0 or higher. Any procedures/non-drug therapies that are incurred during the study will also be coded using MedDRA or World Health Organization (WHO) Drug Enhanced Dictionary, as appropriate. Medical/surgical history will be listed by subject. Procedures/non-drug therapies will be listed by subject, treatment and treatment sequence for the safety population.

5.5 Prior and Concomitant Medications

Prior and concomitant medications will be recorded and coded using the World Health Organization (WHO) Drug Enhanced Dictionary (March 2025 or later).

Prior medications will be those that start and end prior to the first dose of study drug.

A concomitant medication is any medicinal product or substance administered between signing the ICF and the end of study (EOS) or Early Termination (ET) Visit.

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy) performed between obtaining informed consent and the EOS/ET Visit that is not otherwise specified in the protocol

Any concomitant medication taken during the washout period will be assigned to the prior treatment given. Anatomical Therapeutic Chemical (ATC) classification and Preferred Term will be assigned to each record of prior or concomitant medication. All prior and concomitant medications will be listed by subject and by treatment sequence (both prior and concomitant), and treatment (for concomitant), including ATC classification (level 3), preferred term and reported term, the start and end dates (or ongoing status), dose, unit, frequency, route of drug administration, and indication. All concomitant medications administered will be presented in a data listing.

5.6 Pharmacokinetic Analysis

The PK analysis will include plasma concentration data analysis, PK parameters analysis, and relative bioavailability comparison for each subject in the PK population.

5.6.1 Plasma Concentrations

Blood samples will be collected and resulting plasma analyzed to obtain plasma concentrations of HYC, DOX, and their respective metabolites (hydromorphone and 2-keto-doxapram). Plasma concentrations will be listed by subject, treatment sequence and treatment, with both nominal and actual plasma collection point. The plasma will be summarized by treatment at each nominal point of plasma collection using descriptive statistics (n, mean, SD, CV%, geometric mean, geometric CV%, median, min, and max values).

Figures of individual and mean plasma concentration versus nominal time profiles for HYC and metabolite hydromorphone will be produced on semi-log scale for subject in the PK population.

For plasma concentration data, all values below quantification limit (BQL) will be treated as zero in the concentration summary statistics calculation (including plotting). If a sample is missing or the value is not reported and/or is between two measurable concentrations, the value at that time point will be left blank for the analysis and reported as Not Reported (NR).

For PK analysis, plasma concentrations that are BQL will be treated as zero if they occur prior to the first quantifiable concentration on the day of dosing or treated as missing otherwise. Any BQL data points between observed measurable plasma concentrations will be set to missing for PK analysis.

5.6.2 Pharmacokinetic Parameters

Plasma PK parameters for HYC, DOX, and their respective metabolites (hydromorphone and 2-keto-doxapram), will be estimated by non-compartmental analysis (NCA) methods using Phoenix WinNonlin (version 8.1 or higher, Certara USA Inc., Princeton, NJ, USA) and will be based on actual sample collection relative to dose administration.

The following PK parameters will be computed from plasma concentration-time data:

AUC _{0-t}	Area under the plasma concentration-time curve from time zero to the time of last quantifiable concentration, calculated by the linear trapezoidal linear interpolation method
AUC _{0-∞}	Area under the plasma concentration-time curve from time zero extrapolated to infinity, calculated as AUC _{0-t} + C _t /λ _z , where C _t is the last measurable concentration
C _{max}	Maximum plasma concentration
T _{max}	Time to reach the observed maximum (peak) concentration

k_{el}	Terminal elimination rate constant
$t_{1/2}$	Terminal elimination half-life, calculated as $0.693/\lambda_z$
CL/F	Apparent total body clearance of drug from plasma after non-parenteral administration (For HYC and DOX only)
V_d/F	Apparent volume of distribution after non-parenteral administration (For HYC and DOX only)

The C_{max} and T_{max} will be obtained directly from experimental observations. AUC_{0-t} will be estimated using the linear trapezoidal linear interpolation method from time 0 hour to last observed concentration hour.

$AUC_{0-\infty}$ will be calculated as the sum of AUC_{0-t} and $AUC_{t-\infty}$, where t is the time corresponding to the last measurable plasma concentration (t_{last}). $AUC_{t-\infty}$ is defined as the area under the curve from last measurable concentration estimated to infinity and is calculated by C_{last} (plasma concentration at the last quantifiable time point) divided by terminal elimination rate constant (k_{el}).

The value of K_{el} will be estimated by least-squares regression of the terminal log-linear plasma concentration-time profile. The choice of data points used to estimate K_{el} will be determined by the best fit linear method using at least 3 data points past C_{max} being needed for the regression line to be fitted (typically this would be at least the last 3 quantifiable data points representing the terminal elimination phase).

No values for k_{el} , $AUC_{0-\infty}$, CL/F, V_d/F , or $t_{1/2}$ will be reported for cases that do not exhibit a terminal log-linear phase in the concentration-time profile with at least three timepoints past T_{max} (typically this would be at least the last 3 quantifiable data points representing the terminal elimination phase).

If R-squared adjusted is <0.80 , the PK analyst may evaluate whether other time points are more appropriate for the calculation of k_{el} , otherwise k_{el} and PK parameters derived with k_{el} such as $t_{1/2}$, V_d/F and CL/F and $AUC_{0-\infty}$, will not be reported. The R-square adjusted values will be reported in a listing and in the dataset.

For determination of $AUC_{0-\infty}$, if calculated $AUC_{t-\infty}$ is greater than 20% of the calculated AUC from time 0 to infinity, then $AUC_{0-\infty}$ and those PK parameters derived from $AUC_{0-\infty}$ will not be reported. The $AUC_{inf\%}$ extrapolation values will be reported in a listing and in the dataset.

Pharmacokinetic parameters will be listed by subject, treatment sequence, and treatment for all subjects in the PK population. Pharmacokinetic parameters for DOX, HYC and metabolites (hydromorphone and 2-keto-doxapram) will be summarized by treatment using descriptive statistics (n, mean, SD, CV%, geometric mean, geometric CV%, median, min, and max values), except for T_{max} which will be described using min, median, and max.

An additional PK diagnostic listing will be produced for the diagnostic parameters specified above.

5.6.3 Relative Bioavailability Analysis

The relative bioavailability of HYC+DOX to HYC will be evaluated as follows:

- Relative Bioavailability of HYC+DOX (Treatment B, test) versus HYC (Treatment A, reference)

For the above comparison confidence intervals (CIs) will be constructed to test the two one-sided hypotheses at the $\alpha = 0.05$ level of significance for $C_{\max}$, AUC_{0-t} , and $AUC_{0-\infty}$. Natural log-transformed PK parameters $C_{\max}$, AUC_{0-t} , and $AUC_{0-\infty}$ data will be analyzed using an analysis of variance (ANOVA) model with fixed effects for treatment, period and sequence, and a random effect of subject nested in sequence. The geometric mean ratios and 90% confidence intervals for each comparison will be tabulated for $C_{\max}$, $AUC_{(0-t)}$ and $AUC_{0-\infty}$, where the geometric mean ratios are defined as “HYC+DOX / HYC”. This may be an unbalanced model due to possible observed subject differences between PK parameters reported by treatment.

The relative bioavailability will be established if the 90% CIs for the ratio of the population geometric means between test and reference treatment, based on natural log-transformed data, is contained within the equivalence limits of 80.00-125.00% for $C_{\max}$, AUC_{0-t} , and $AUC_{0-\infty}$ (if applicable).

5.7 Safety Analysis

All safety summary tables (as applicable) and listings will be presented.

Safety will be assessed by the incidence of AEs and TEAEs, study discontinuation information, physical examinations, clinical laboratory evaluations, ECGs, and vital signs measurements.

Safety variables will be tabulated (where applicable) and presented for all participants in the safety population. Adverse events will be summarized by MedDRA system organ class, preferred term, and treatment. All safety assessments will be listed.

5.7.1 Study Product Exposure

Exposure to study drug will be listed by subject, treatment sequence, and treatment received, indicating dose date and time. Any deviations will be documented as specified under the Protocol Deviations section and listed separate from the study exposure.

5.7.2 Adverse Events

All AEs occurring during the study, from the signing of informed consent to approximately 7 days following the last study drug administration, including the washout intervals, will be documented on the eCRF. All AEs will be coded and classified using the Medical

Dictionary for Regulatory Activities (MedDRA) v28.0 or higher. The severity of adverse events is determined by the Investigator using the Common Terminology Criteria for Adverse Events (CTCAE v5.0) (refer to the protocol) as mild, moderate, severe, and the relationship to study drug is determined by the Investigator as definite, probable, possible, unlikely or not related. Adverse events which occur prior to the date and time of the first dose of study drug are considered non-treatment emergent events. Adverse events which occur on or after the date and time of the first dose of study drug up to approximately 7 days following the last drug administration are considered treatment emergent adverse events. Adverse events occurring during a treatment period will be summarized under the treatment received when the AE started. Adverse events that occur during a washout period will be attributed to the prior treatment.

All TEAEs will be summarized as the number and percentage of subjects by System Organ Class, Preferred Term, and treatment. Separate summaries will be created by severity and by relationship to study drug. If the same AE (preferred term) is reported more than once for the same subject, it will only be counted once in the summary table. For summary tables by severity and relationship to study drug, if the same AE (preferred term) is reported more than once for the same subject, the highest severity grade (severe > moderate > mild) or the strongest relationship to treatment (related > possibly related > unrelated) will be counted in the summary table.

All AEs will be listed, and those that are treatment-emergent will be identified.

All Serious Adverse Events (SAEs) including any deaths will be listed by subjects.

All AEs leading to study discontinuation will be listed by subjects.

5.7.3 Clinical Laboratory Assessments

Clinical laboratory test parameters (refer to [Table 2](#)), with associated reference ranges provided by the laboratory, will be listed for individual subjects by treatment sequence and time point. Clinical laboratory test results outside the laboratory's reference ranges will be flagged with "L" for low and "H" for high.

The summary may be produced for blood chemistry and hematology numeric tests only, and would include descriptive statistics for baseline, all post-baseline, and change from baseline values by treatment sequence.

Table 2: Clinical Laboratory Tests

Laboratory Tests ¹	Parameters	
Hematology	Complete blood count (CBC) with differential	WBC differential: <ul style="list-style-type: none"> Neutrophils Eosinophils Basophils Lymphocytes
	White blood cell count (WBC)	
	Red blood cell (RBC) count	
	Hemoglobin (Hgb)	

	Hematocrit (Hct)		● Monocytes
	Platelet count (Plt)		
Serology	Hepatitis B Surface Antigen test (HBsAg)	Hepatitis C virus (HCV)	Human immunodeficiency virus (HIV)
Serum Chemistry	Sodium (Na)	Creatinine (Cr)	Alanine aminotransferase (ALT, SGPT)
	Potassium (K)	Uric acid	Aspartate aminotransferase (AST, SGOT)
	Chloride (Cl)	Albumin	Calcium (Ca)
	Bicarbonate (HCO ₃)/CO ₂	Total protein	Phosphate (PO ₄)
	Glucose	Total and indirect bilirubin	Lactate dehydrogenase (LDH)
	Blood urea nitrogen (BUN) (Urea in AUS)	Alkaline phosphatase	
Urinalysis	Specific gravity	pH	Leukocytes
	Nitrite	Protein	Glucose
	Ketones	Bilirubin	Blood
	Urobilinogen	Microscopy (when needed)	
Pregnancy Testing ²	Highly sensitive serum human chorionic gonadotropin (hCG) pregnancy test within 7 days prior to Day 1 and urine test upon admission on Day 1.		
Hormone Testing	Follicle-stimulating hormone (FSH) and estradiol levels at screening as needed to confirm menopause).		
Drug of Abuse Screening	Urine drug of abuse screen, includes amphetamines, methamphetamines, methadone, barbiturates, benzodiazepines, cocaine, opioids, methylenedioxymethamphetamine, phencyclidine, cotinine, alcohol breath test, tetrahydrocannabinol (THC) and cannabinoids.		

1. Lab test panels from local labs may contain additional lab results.
2. In women of childbearing potential, as defined in Section 10.4.1 in the protocol.

5.7.4 Vital Signs Assessments

Vital signs, including systolic and diastolic blood pressure, pulse rate, respiratory rate, and blood oxygen saturation (pulse oximetry), and oral temperature are measured at the time points indicated in the SoA (Table 1). Vital signs (except for height and weight and BMI collected at Screening only) will be monitored periodically during and following study of drug administration. The investigator may repeat the vital signs if deemed appropriate.

All assessments will be listed by subject, treatment sequence, and visit.

A summary table will be produced and will include descriptive statistics for baseline, post-baseline, and change from baseline values by treatment sequence for each vital sign parameter (this will not include BMI which is calculated at screening).

5.7.5 Physical Examinations

A complete physical examination (PE) will be conducted at the time points designated in the schedule of assessments (SoA) (Table 1). At other designated time points, a partial (symptom-directed) physical examination may be conducted. Complete physical examination includes height, weight, vital sign, systems/organs to examine include skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular, abdomen, lymph nodes, and musculoskeletal system/extremities, and a targeted physical may be performed as needed during the study to assess any adverse events.

Physical examinations may be repeated prior to study discharge as deemed necessary by the Investigator or in response to AE.

Physical examination results will be listed by subject, treatment, and visit.

5.7.6 Electrocardiogram

12-lead ECGs will be recorded after the subject has been resting for at least 5 minutes in the supine or semi-recumbent position at the timepoints specified in the SoA (Table 1). The ECG will be obtained at approximately the same time on study Days 2 and 4 to minimize differences due to circadian variations. The treatment Day 2 and 4 assessments will each be associated with PK blood samples.

Electrocardiogram assessments will include comments on whether the tracings are normal or abnormal, rhythm, presence of arrhythmia or conduction defects, morphology, any evidence of myocardial infarction, or ST segment, T wave, and U wave abnormalities. In addition, measurements of the following intervals will be measured and reported: RR interval, PR interval, QRS width, QT interval, and QT interval corrected for heart rate using Fridericia's formula (QTcF). The date and time of each ECG and its results will be documented in the source documents and transcribed into the eCRF.

Electrocardiograms may be performed at any time during the study in the interest of subject's safety at the discretion of the Investigator.

The overall interpretation of the ECG result will be presented as normal, abnormal (not clinically significant) and abnormal (clinically significant) for each day, by treatment sequence. Descriptive statistics will be presented for the ECG measurements and change from baseline collected each day by treatment sequence.

The ECG parameters will be listed by subject, treatment sequence, and visit.

5.8 Pharmacodynamic Analysis

Pharmacodynamic analyses will be performed using the PD population.

Richmond Agitation Sedation Scale values will be listed and summarized by treatment and time points for all subjects in the PD Population and values will be presented with the same level of precision as received from the clinical laboratory database.

A summary table will be produced for Richmond Agitation Sedation Scale (RASS) at scheduled timepoints with descriptive statistics including n, Mean, SD, CV%, minimum, median, and maximum.

The level of precision for the RASS values summary statistics will be presented as follows:

- minimum/maximum: in same precision as in the clinical laboratory database
- Mean/median: in one more level of precision than minimum/maximum
- SD: in one more level of precision than mean/median
- n will be presented as an integer
- CV% will be presented to the nearest tenth

5.9 Interim Analysis

No interim analysis is planned.

5.10 Statistical Programming and Deliverables

All statistical analyses, tables, and listings will be generated in SAS (version 9.4 or later) with appropriate documentation and programming validation. The table of contents of all tables, listings, and figures will be presented in a TLFs shell supplemental document.

5.11 Changes to the Planned Analysis

Any deviation(s) of consequence from the SAP during the data analysis will be documented and justified in an amended SAP and/or in the final report or addressed in a separate document (such as the Clinical Study Report), as appropriate.

6 Revision history (for any changes post-Final SAP)

Version	Date	Comments