



CLINICAL STUDY PROTOCOL

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

Protocol Number: QEV-817-101

Version/Amendment Number: Version 7.1

Version Date: 23 Sept 2025

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Investigational Product: QEV-817

Development Phase: Phase 1

Brief Title: Safety and Pharmacokinetics of QEV-817 Oral Suspension (QEV-817-S)

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Refer to [Appendix 5](#) for Information on the Management of Medical Emergencies

SPONSOR SIGNATORY

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Protocol accepted and approved by:

John Hsu, MD
Chief Medical Officer

Quivive Pharma, Inc.
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Signature

Date

INVESTIGATOR SIGNATURE

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By signing below, I agree that:

I have read this protocol and agree that it contains all necessary details for carrying out the study as described. I will conduct this study in accordance with the design and specific provision of this protocol. I will not initiate the study until it has received approval from the Institutional Review Board/Ethics Committee. I will provide copies of this protocol and access to all information furnished by Quivive Pharma, Inc. to study personnel under my supervision. I will discuss this material with them to ensure they are fully informed about the study product and study procedures, and further inform them of its confidential and proprietary nature and that it may not be disclosed to third parties. I understand that the study may be terminated, or enrollment suspended, at any time by Quivive Pharma, Inc. with or without cause, or by me if it becomes necessary to protect the best interests of the study patients.

I agree to conduct this study in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the International Council for Harmonisation guidelines for Good Clinical Practice, and applicable regional regulations.

INVESTIGATOR SIGNATURE

Investigator Signature

Date

Investigator Printed Name

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LIST OF ABBREVIATIONS

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
ARCI	Addiction Research Center Inventory
AST	aspartate aminotransferase
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 the time of the last quantifiable concentration
BLQ	below the limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CFR	Code of Federal Regulations
CL/F	apparent total body clearance of the drug from plasma
C _{av}	mean steady state drug concentration
CIOMS	Council for International Organizations of Medical Sciences
C _{max}	maximum plasma concentration
C _{min}	trough plasma concentration
CNS	central nervous system
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form
CRU	Clinical Research Unit
CTCAE	common terminology criteria for adverse events
CV	coefficient of variation
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DOX	doxapram hydrochloride
DOX-DP	doxapram drug product
EDC	electronic data collection
ECG	electrocardiogram
ET	early termination
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GMR	geometric mean ratio
HBsAg	hepatitis B surface antigen
hCG	human chorionic gonadotropin
HCT	hematocrit
HCV	hepatitis C virus
HGB	hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HYC	hydrocodone bitartrate

Abbreviation	Term
HYC-DP	hydrocodone drug product
HYC-S	control; hydrocodone oral suspension
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Institutional Ethics Committee
IND	Investigational New Drug
IR	Immediate-release
IRB	Institutional Review Board
ISRC	Independent Safety Review Committee
IUD	Intrauterine device
k_{el}	apparent elimination rate constant
K_i	inhibition constant
LDH	lactic acid dehydrogenase
LLN	lower limit of normal
MAOI	monoamine oxidase inhibitor
MDE	minimum detectable effect
MedDRA	Medical Dictionary for Regulatory Activities
MTD	maximum tolerated dose
NHP	non-human primate
NSAID	non-steroidal anti-inflammatory drugs
OTC	over-the-counter
PD	pharmacodynamics
PK	pharmacokinetics
QEV-817-S	Phase 1 clinical trial material and investigational product; QEV-817 oral suspension
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SoA	Schedule of Activities
SOP	standard operating procedure
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	elimination half-life
TBD	to be determined
TEAE	treatment-emergent adverse event
T_{max}	time to reach the observed maximum (peak) concentration
ULN	upper limit of normal
US	United States
USP	United States Pharmacopeia
VAS	visual analog scale
V_d/F	apparent volume of distribution
w/v	weight-per-volume
WBC	white blood cell

Abbreviation	Term
WOCBP	women of childbearing potential
WONCBP	women of non-childbearing potential

1.0 PROTOCOL SUMMARY

1.1 Synopsis

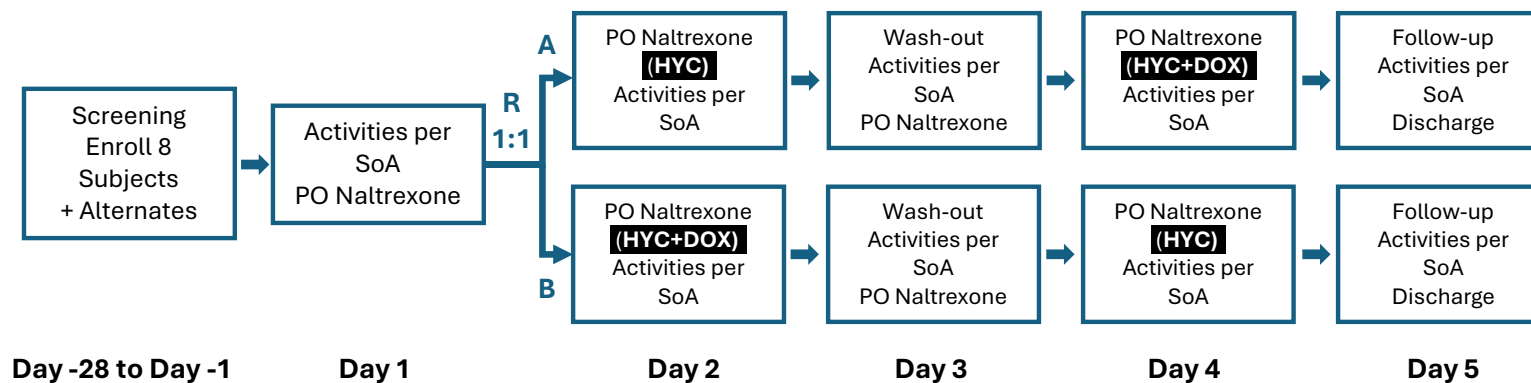
Protocol Number: QEV-817-101	Version: 7.0	For National Authority Use Only
IND Number: 133387	EU CT Number: not applicable	
Sponsor: Quivive Pharma, Inc.		
Investigational Product: QEV-817		
Title of Study: A Phase 1, Randomized, Open Label, Crossover Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of QEV-817 Oral Suspension in Healthy Volunteers		
Brief Title: Safety and Pharmacokinetics of QEV-817 Oral Suspension (QEV-817-S)		
Brief Study Rationale: <p>The doxapram hydrochloride (DOX) component of QEV-817 is intended to mitigate respiratory depression associated with hydrocodone and to act as an abuse-deterrent when the product is overconsumed for purposes of abuse or misuse. Thus, this study has been designed to assess the safety, tolerability, and PK of a 10 mg therapeutic dose of hydrocodone (HYC) with and without oral DOX (50 mg) in healthy volunteers who are naltrexone-blocked.</p>		
Type of Study/Development Phase: Human pharmacology/Phase 1	Countries/Regions: US	
Study Period: Approximately one (1) year		
Objectives and Key Endpoints:		
Objectives	Endpoints	
Primary		
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)	<ul style="list-style-type: none"> Nature, severity, and incidence of AEs Changes from baseline in physical examination, vital signs, 12-lead ECG assessment, pulse oximetry, and clinical laboratory tests 	
Secondary		
<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> 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, 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}). 	
Exploratory		
To explore responses on the Richmond Agitation Sedation Scale (RASS)	<ul style="list-style-type: none"> RASS score as assessed by physician 	

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Title of Study: A Phase 1, Randomized, Open Label, Crossover Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of QEV-817 Oral Suspension in Healthy Volunteers											
Design/Methodology/Measures to Minimize Bias: <p>This is a Phase 1, single-center, open label, randomized crossover study that will be conducted in male and female healthy volunteers. The study will be conducted at a single site in the US. The study consists of a 28-day Screening Period, a four-day treatment period, and a one-day safety follow-up period.</p> <p>The study will be conducted in eight (8) healthy male and female subjects. Up to an additional five (5) subjects may be enrolled as alternates to replace dropouts. Subjects will be randomized (1:1) to one of two crossover treatment sequences as follows:</p> <table border="1"> <thead> <tr> <th>Sequence Number</th> <th>Treatment Day 2</th> <th>Treatment Day 4</th> </tr> </thead> <tbody> <tr> <td>Sequence A</td> <td>HYC</td> <td>HYC+DOX</td> </tr> <tr> <td>Sequence B</td> <td>HYC+DOX</td> <td>HYC</td> </tr> </tbody> </table> <p>Subjects will receive either a fixed therapeutic dose of oral HYC of 10 mg alone (HYC) or in combination with a fixed dose of 50 mg oral DOX (HYC+DOX). Prior to treatment with HYC or HYC+DOX, all subjects will receive naltrexone (opioid antagonist) to block opioid effects (i.e., naltrexone block).</p>			Sequence Number	Treatment Day 2	Treatment Day 4	Sequence A	HYC	HYC+DOX	Sequence B	HYC+DOX	HYC
Sequence Number	Treatment Day 2	Treatment Day 4									
Sequence A	HYC	HYC+DOX									
Sequence B	HYC+DOX	HYC									
Number of Participants Planned: Approximately eight (8) healthy volunteers	Gender: Male or female	Age: 18–55 years, inclusive									
Key Criteria for Eligibility: <p>The study will include male or female healthy volunteer adults who have never used opioids for non-therapeutic purposes (i.e., for recreational effects). Subjects with a history of valid medical use under prescription must have not used an opioid for at least three (3) months prior to Day 1. Refer to Protocol Section 5.1 for a complete list of inclusion criteria.</p> <p>Female subjects who are pregnant or lactating are excluded. Subjects with a positive urine drug, cotinine, or alcohol test at screening or upon admission, excluding tetrahydrocannabinol (THC) or cannabinoid metabolites, are also excluded. Refer to Protocol Section 5.2 for a complete list of exclusion criteria.</p>											
Total Participant Duration: Up to 33 days	Treatment Duration: 4 days										
Investigational Product, Dose, and Route of Administration: QEV-817 (10 mg HYC+50 mg DOX), oral suspension	Control, Dose, and Route of Administration: 10 mg HYC, oral suspension										
Pharmacokinetics Evaluation: <p>DOX plasma PK parameters will include (but are 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.</p> <p>HYC plasma PK parameters will include (but are not limited to): C_{max}, T_{max}, $AUC_{0-\infty}$, AUC_{0-t}, V_d/F, CL/F, and $t_{1/2}$ of HYC and its active metabolite hydromorphone.</p>											
Pharmacodynamics Evaluation: <p>A Richmond Agitation Sedation Scale (RASS) will be used to assess exploratory pharmacodynamic objectives.</p>											

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Title of Study: A Phase 1, Randomized, Open Label, Crossover Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of QEV-817 Oral Suspension in Healthy Volunteers		
Safety Evaluation: Safety will be evaluated by monitoring the nature, severity, and incidence of adverse events (AEs); and changes from baseline in physical examination, vital signs, 12-lead ECG assessment, pulse oximetry, and clinical laboratory tests.		
Study Hypothesis and Statistical Considerations: A formal statistical hypothesis is not available for this Phase 1 study. Data listings will be provided for safety, PK and pharmacodynamic (PD) data and parameters. Summary statistics will be provided for safety data, PD, and PK data and parameters by dose level and/or treatment. For continuous variables, descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum) will be provided. For categorical variables, subject counts and percentages will be provided. Tabulations will be presented by dose level. All study data will be presented by subject in data listings. 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. Subject disposition will be summarized 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. <u>Sample Size Determination</u> To support the PK comparison of HYC with and without co-administration with DOX, a sample size of eight (8) subjects was determined by statistical analysis of the minimum detectable effect (MDE) for a clinical PK interaction for HYC. This was based on the reported variability in the plasma PK of oral HYC in human subjects using natural log transformed values of the three (3) primary pharmacokinetic (PK) parameters: C_{max} , $AUC_{(0-t)}$, and $AUC_{(inf)}$. C_{max} was found to have the highest variability of the three (3) primary pharmacokinetic (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 of natural log C_{max} ; i.e., a minimum increase in C_{max} of essentially 50% may be statistically detected using eight (8) subjects.		
Version (Date): Version 7.1 (23 Sept 2025)		

1.2 Study Schema

Figure 1: Protocol QEV-817-101: Study Schema



Abbreviations: DOX = doxapram; HYC = hydrocodone; HYC+DOX = QEV-817 oral suspension; R = randomization; SoA = Schedule of Activities.

1.3 Schedule of Activities

Table 1: Protocol QEV-817-101: Schedule of Activities

Study Stage/Period	Screening	Treatment				Follow-up
	Day -28 to -1	Day 1	Day 2	Day 3	Day 4	Discharge Day 5/ET
Study Day						
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](#).
- b. **Medical history/demographics:** refer to [Section 8.1.1](#).
- 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 (ie. on study Day 3 and prior to discharge on study Day 5). Refer to [Section 8.2.2](#).
- 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](#).
- 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](#)), except for tetrahydrocannabinol (THC) or cannabinoid metabolites. Refer to [Section 8.1.3](#).
- 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](#).
- i. **Vital signs:** includes 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](#).
- 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](#).
- 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 $\pm$ 1 hours prior to Day 2 and Day 4 study drug administrations.
 - Days 2 and 4: 60 $\pm$ 15 minutes prior to study drug administrations.
- n. **Study drug administration:** Refer to [Sections 4.1.1](#) and [6.1](#). 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](#)):

- 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-hours post-dose ($\pm$ 5 minutes for 0.25 to 4 hours; $\pm$ 15 min for 6 to 12 hours);
 - Days 3 and 5: approximately 24 hours after study drug administration ($\pm$ 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 ($\pm$ 10 minutes). Refer to [Section 8.1.5](#).
- 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](#).

2.0 INTRODUCTION

-----[REDACTED]-----

2.1 Study Rationale

-----[REDACTED]-----

Thus, this study has been designed to assess the safety, tolerability, and PK of a therapeutic dose of HYC (10 mg) with and without oral DOX (50 mg) in healthy volunteers who are naltrexone-blocked.

2.2 Background

2.2.1 Acute Pain

Acute pain usually is associated with tissue injury, inflammation, a surgical procedure, trauma, or a short-term disease process. The 2012 National Health Interview Survey (NHIS) revealed that 56% of adults in the US reported some pain during the previous 3 months ([Nahin 2015](#)). The major factor in acute pain management is deciding on an appropriate intervention and/or analgesic that will provide the best pain relief to the patient.

2.2.2 Current Therapies for Acute Pain Management

2.2.2.1 Overview of Treatment Options

In addition to regional anesthesia and non-pharmacological interventions, pharmacologic options for acute pain include the following: non-steroidal anti-inflammatory drugs (NSAIDs), acetaminophen, opioids, ketamine, gabapentinoids, alpha-2 agonists, cannabinoids, and intravenous lidocaine.

2.2.2.2 Opioids

Opioids have long been the cornerstone treatment for moderate to severe acute pain, having formally been approved in the United States (US) for analgesia for close to 70 years, and for the most part, these drugs have been assumed to be relatively safe ([Schiller 2023](#)). However, in the last two decades, many reports have raised concern about the safety of these drugs during a period of dramatic increases in opioid prescriptions. This empirical prescription habit by healthcare workers has also led to an epidemic of overdoses outside of the healthcare setting ([Schiller 2023](#)).

2.2.2.2.1 Efficacy and Safety

The US Centers for Disease Control and Prevention (CDC) reports that drug overdose deaths and opioid-involved deaths continue to increase in the United States. The majority (more than 60%) of drug overdose deaths in the US involve an opioid. Since 1999, the number of overdose deaths involving opioids, including prescription opioids and heroin quadrupled from 1.4 per 100,000 to

5.4 per 100,000 ([Murphy 2013](#); [Rudd 2016](#)); deaths from HYC products, specifically, have more than quadrupled since 1999 ([Ossiander 2014](#)). Unfortunately, it is estimated that 91 Americans die every day from an opioid overdose ([Rudd 2016](#)). It is now apparent that overdoses from prescription opioids are a driving factor in the 15-year increase in opioid overdose deaths. From 1999 to 2014, sales of prescription opioids in the US nearly quadrupled (from approximately 1.7 kg per 10,000 population to 7 kg per 10,000 population; rates vary by state ([Paulozzi 2011](#))), yet there has not been an overall change in the amount of pain that Americans report. For example, in an analysis of serial cross-sectional data regarding emergency department visits from 2000–2010, from the National Hospital Ambulatory Medical Care Survey, rates of reported pain remained stable, representing approximately 45% of visits across 10 years ([Chang 2014](#); [Daubresse 2013](#)).

2.2.2.2.2 Respiratory Depression Due to Opioids

The primary cause of death from opioid overdose is lethal respiratory depression ([Bhardwaj 2014](#); [Dahan 2010](#); [White 1999](#)). Respiratory depression is the most serious opioid adverse reaction and is most concerning when large opioid doses are ingested by opioid-naïve individuals with severe pain (especially if this pain is short-lived or self-resolving).

Limitations on access to opioids has increased the number from 48 in 2013 to 91 in 2015 people dying per day. The current policy to limit legally prescribed opioids will have a limited effect, because 60% of patients misusing the drugs were using opioids without a prescription, according to the report published in the Annals of Internal Medicine ([Han 2017](#)). About 40% of these people accessed opioids free from friends or relatives. Among people who developed addiction or other abuse disorders, 14% said they bought them from drug dealers or strangers. Clearly, a method to make opioids safe from respiratory depression is needed no matter who takes the opioid.

2.2.2.2.3 Unmet Need and Product Development Rationale

-----[REDACTED]-----

2.2.2.2.4 Doxapram as -----[REDACTED]-----

-----[REDACTED]-----

2.2.3 Description of QEV-817

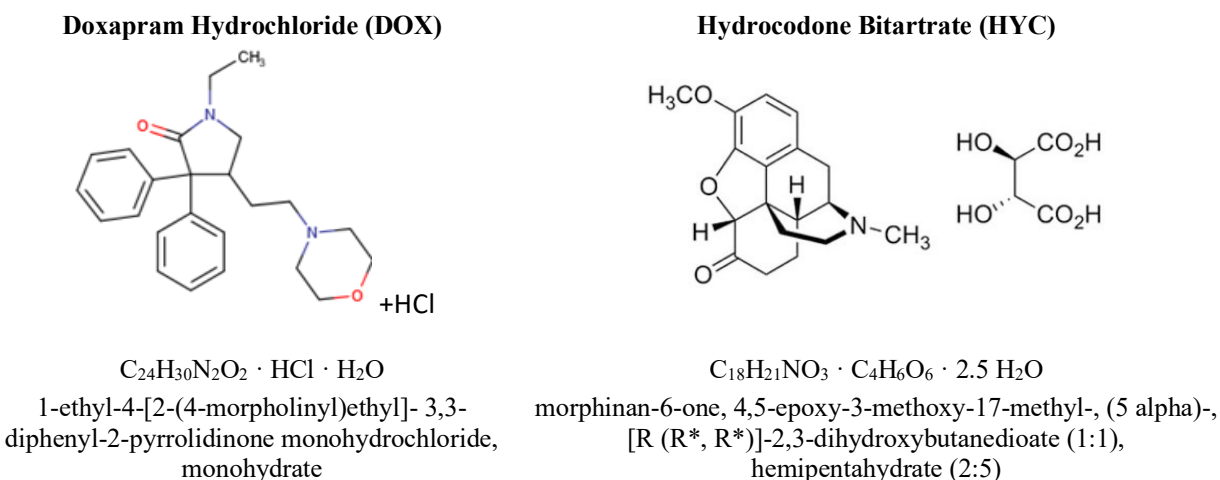
-----[REDACTED]----- The Phase 1 clinical trial material, QEV-817-S, will be an aqueous oral suspension of HYC+DOX. -----[REDACTED]----- HYC-S refers to the Phase 1 clinical trial material, which is an aqueous oral suspension of HYC only (HYC-S). Additional details on the Phase 1 study treatments are provided in [Section 6.0](#).

HYC and DOX are described below and the structure of each is provided in [Figure 2](#).

HYC is a full opioid agonist with relative selectivity for the mu-opioid receptor, although it can interact with other opioid receptors at higher doses. The principal therapeutic action of HYC is analgesia. Like all full opioid agonists, there is no ceiling effect for analgesia with HYC. Clinically, dosage is titrated to provide adequate analgesia and may be limited by adverse reactions, including respiratory and CNS depression. The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and are thought to play a role in the analgesic effects of this drug (Hysingla® ER USPI).

DOX produces respiratory stimulation mediated through the peripheral carotid chemoreceptors. As the dosage level is increased, the central respiratory centers in the medulla are stimulated with progressive stimulation of other parts of the brain and spinal cord. The respiratory stimulant action is manifested by an increase in tidal volume associated with a slight increase in respiratory rate. A pressor response may result following DOX administration. Provided there is no impairment of cardiac function, the pressor effect is more marked in hypovolemic than in normovolemic states. The pressor response is due to the improved cardiac output rather than peripheral vasoconstriction. Following DOX administration, an increased release of catecholamines has been noted. Although opioid-induced respiratory depression is antagonized by DOX, the analgesic effect is not affected (Dopram® USPI).

Figure 2: Structure of Doxapram Hydrochloride and Hydrocodone Bitartrate



A detailed description of the chemistry, mechanism of action and nonclinical information related to QEV-817 and its components is provided in the QEV-817 Investigator's Brochure (IB).

2.3 Benefit/Risk Assessment

2.3.1 Potential Benefits

For patients with the need for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, QEV-817 may provide opioid-

equivalent analgesia with a significantly reduced risk of death or morbidity in case of accidental or intentional overdose. The proposed combination will have the added benefit of an effective abuse deterrence, reducing or eliminating non-medical diversion of the product. Thus, this study has been designed to assess the initial PK and tolerability of QEV-817.

2.3.2 Potential Risks

There are risks inherent to the pharmacological properties and study procedures in Study QEV-817-101. Clinically significant potential risks and their mitigation strategies are summarized in Table 2.

Table 2: Protocol QEV-817-101: Potential Risks and Mitigation Strategies

Potential Risk	Rationale for Risk	Phase 1 Risk Mitigation Strategy (Protocol QEV-817-101)
Study Intervention(s)		
Excessive CNS and respiratory depression due to opioid administration	<ul style="list-style-type: none"> All opioid-based medicinal products carry a risk of excessive respiratory depression. -----[REDACTED]----- Concomitant use of CYP3A4 inhibitors may increase hydrocodone plasma concentrations, which could increase or prolong adverse reactions and may cause potentially fatal respiratory depression (Hysingla ER USPI). 	<p>A 10 mg therapeutic dosage level of HYC will be used under naltrexone block. All subjects will receive oral naltrexone (i.e., naltrexone block) both 12 ± 1 hours and 1 hour $\pm$ minutes prior to administration of HYC on both treatment days.</p> <p>All subjects will be monitored for at least 24 hours after study drug administration. Rigorous safety assessments and adverse event monitoring and a medical emergency plan have been implemented. Subjects will undergo vital sign and pulse oximetry monitoring, there will be stopping rules for the treatment and rescue medications will be present.</p> <p>In all QEV-817 studies, naloxone, a narcotic antagonist, will be readily available and will be administered intravenously or intranasally at the Investigator's medical discretion to reverse excessive CNS and respiratory depression that could occur because of opioid administration.</p> <p>In all QEV-817 studies, use of any CYP3A4 inhibitors or inducers is prohibited within 7 days prior to the first treatment and throughout the treatment and follow-up periods.</p> <p>In the ICF for all QEV-817 studies, subjects will be warned that opioids such HYC may cause life-threatening respiratory depression.</p>

Potential Risk	Rationale for Risk	Phase 1 Risk Mitigation Strategy (Protocol QEV-817-101)
Severe hypotension due to opioid administration	<ul style="list-style-type: none"> All opioid-based medicinal products carry a risk of hypotension. 	<p>A 10 mg therapeutic dosage level of HYC will be used under naltrexone block (i.e., all subjects receive oral naltrexone both 12 hours prior and 1 hour prior to administration of HYC on both treatment days) to mitigate any opioid effects.</p> <p>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 various timepoints after study treatment administration.</p> <p>All subjects will be monitored for at least 24 hours after study drug administration. Rigorous safety assessments and adverse event monitoring and a medical emergency plan have been implemented. Subjects will undergo vital sign and pulse oximetry monitoring, there will be stopping rules for the treatment and rescue medications will be present.</p> <p>In all QEV-817 studies, naloxone, a narcotic antagonist, will be readily available and will be administered intravenously or intranasally at the Investigator's medical discretion to reverse excessive opioid exposure.</p> <p>In the ICF for all QEV-817 studies, subjects will be warned that opioids such HYC may cause low blood pressure.</p>
Gastrointestinal adverse reactions due to opioid or DOX administration	<ul style="list-style-type: none"> DOX and opioids are associated with gastrointestinal adverse reactions (DOPRAM Injection USPI; Hysingla ER USPI). 	Subjects will be intensively monitored for at least 24 hours after study drug administration. Rigorous safety assessments and adverse event monitoring have been implemented.
Prolongation of the QTc interval due to opioid or DOX administration	<ul style="list-style-type: none"> DOX and opioids are associated with a risk of prolongation of the QTc interval (DOPRAM Injection USPI; Hysingla ER USPI). The labeling for intravenous Dopram includes warnings of a risk for ventricular tachycardia and ventricular fibrillation, however these are presented in the context of postanesthetic use with volatile agents known to sensitize the myocardium to catecholamines. 	Subject vital signs will be monitored for at least 24 hours after study drug administration, including 12-lead ECGs at numerous time-points post-administration. Rigorous safety assessments and adverse event monitoring have been implemented.

Potential Risk	Rationale for Risk	Phase 1 Risk Mitigation Strategy (Protocol QEV-817-101)
CNS hyperexcitation due to DOX administration	<ul style="list-style-type: none"> Intravenous DOX is associated with symptoms of sympathetic or CNS hyperexcitation (DOPRAM Injection USPI). 	<p>Subject vital signs will be monitored for at least 24 hours after study drug administration. Rigorous safety assessments and adverse event monitoring have been implemented. Symptoms of clinically significant sympathetic or CNS hyperexcitation will be treated with midazolam, propofol, or dexmedetomidine as deemed clinically appropriate by the Investigator and the subject will be discontinued from study treatment.</p> <p>In all QEV-817 studies, the following subjects are excluded:</p> <ul style="list-style-type: none"> Those currently taking monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, sympathomimetic drugs, neuromuscular blocking agents, narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants. Those with active (or history of) epilepsy, seizure disorder, serious head injury, cerebral vascular accident, cerebral edema, or severe hypertension.
Addiction, abuse, and/or misuse	<ul style="list-style-type: none"> QEV-817 contains hydrocodone, a Schedule II controlled substance. As an opioid, QEV-817 exposes users to the risks of opioid addiction, abuse, and misuse. 	<p>A 10 mg therapeutic dosage level of HYC will be used under naltrexone block. All subjects will receive oral naltrexone (i.e., naltrexone block) both 12 ± 1 hours and $1 \text{ hour} \pm \text{minutes}$ prior to administration of HYC.</p> <p>Study treatment administration will occur only under direct supervision in a dedicated clinical research unit. Study treatment may only be supplied or administered by authorized site staff. All study intervention will be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions/manufacturer's instructions, with access limited to only the pharmacist or designee.</p> <p>In the ICF for all QEV-817 studies, subjects will be warned that abuse or misuse of opioids such as HYC may result in dependency.</p>
Phase 1 Study Population		

Potential Risk	Rationale for Risk	Phase 1 Risk Mitigation Strategy (Protocol QEV-817-101)
No direct benefit to healthy volunteers	<ul style="list-style-type: none"> As with all human pharmacology studies in healthy volunteers, this study will have no direct benefit to participants. 	<p>Subjects will be informed that participation in a human PK study will not be of benefit to healthy volunteers. Nevertheless, the information from the physical examination, vital sign measurements, and ECG results may be shared with the subject's personal physician if this is the subject's choice. Subjects will be informed that it is also their choice to inform their personal physician that they are participating in this research study.</p> <p>Subjects will be informed that their contribution to the study is important to helping clinicians understand the potential for minimizing the dangerous respiratory depressive effects of opioids by co-administration with respiratory stimulants. However, because this is a study in healthy volunteers, subjects will be informed that they have the alternative not to participate.</p>
Phase 1 Study Procedures		
Catheter site reactions such as soreness, bruising, or infection	<ul style="list-style-type: none"> As with all studies utilizing intravenous administration and/or blood sampling, participants in this study are at risk of catheter site reactions. 	Subjects will be informed that insertion of an IV catheter will be required for collection of repeated blood samples and possible administration of rescue medications if needed, and that soreness, bruising or infection at the insertion site are possible but unlikely.
Study-continuity issues (e.g., pandemics)	<ul style="list-style-type: none"> International guidelines (e.g., FDA Guidance on Conduct of Clinical Trials of Medical Products During the COVID 19 Public Health Emergency) on the conduct of clinical trials during the COVID 19 pandemic. 	<p>Local measures have been developed. The SoA has been optimized to allow for adequate follow-up and assessment of the study objectives without unnecessarily increasing subject exposure.</p> <p>Alternate strategies for subject visits, assessments, treatment distribution, and monitoring may be implemented by the Sponsor or the Investigator, as per local health authority/ethics requirements.</p>

2.3.3 Benefit/Risk Conclusion

The potential benefits of understanding the safety, tolerability, and PK of QEV-817 in healthy volunteers have been considered against the risks associated with QEV-817 and study procedures. Risk mitigation strategies are in place to address all known potential risks.

For patients with the need for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate, QEV-817 will provide opioid-equivalent analgesia with a significantly reduced risk of death or morbidity in case of accidental or intentional overdose. -----[REDACTED]----- . Therefore, the Sponsor considers that the value of information to be gained outweighs the risks associated with participation in this study.

3.0 OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
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)	<ul style="list-style-type: none"> Incidence, nature, and severity of AEs Changes from baseline in physical examination, vital signs, 12-lead ECG assessment, pulse oximetry, and clinical laboratory tests
Secondary	
<ul style="list-style-type: none"> 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 	<ul style="list-style-type: none"> Plasma PK parameters including (but are 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 are not limited to): C_{max}, T_{max}, $AUC_{0-\infty}$, AUC_{0-t}, V_d/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}).
Exploratory	
To explore responses on the Richmond Agitation Sedation Scale (RASS)	<ul style="list-style-type: none"> RASS score as assessed by physician

Abbreviations: AEs = adverse events; AUC_{0-t} = area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration; $AUC_{0-\infty}$ = area under the plasma concentration-time curve from time zero extrapolated to infinity; CL/F = apparent total body clearance of the drug from plasma; C_{max} = maximum plasma concentration; ECG = electrocardiogram; T_{max} = time to reach the observed maximum (peak) concentration; V_d/F = apparent volume of distribution.

4.0 STUDY DESIGN

4.1 Overall Design

This is a Phase 1, single-center, open label, randomized crossover study that will be conducted in male and female healthy volunteers. The study will be conducted at a single site in the US. The study consists of a 28-day Screening Period, a four-day treatment period, and a one-day safety follow-up period. Thus, the total participant duration is up to approximately 33 days.

The primary objective of this study is 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. This study will be conducted in eight (8) healthy male and female subjects. Up to an additional five (5) subjects may be enrolled as alternates to replace dropouts. Subjects will be randomized (1:1) to one of two crossover treatment sequences provided in [Table 3](#). Subjects will receive either a fixed therapeutic dose of oral HYC of 10 mg alone (HYC) or in combination with a fixed dose of 50 mg oral DOX (HYC+DOX). Prior to treatment with HYC or HYC+DOX, all subjects will receive naltrexone (opioid antagonist) to block opioid effects (i.e., naltrexone block). The Study Schema is provided in [Section 1.2](#). The Schedule of Activities (SoA) is provided in [Section 1.3](#).

After signing informed consent, each subject will be evaluated for study eligibility during the Screening Period (Day -28 to Day -1). Subjects confirmed as eligible will be randomized in a 1:1 ratio to one of two treatment sequences as shown in [Table 3](#).

Table 3: Protocol QEV-817-101: Treatment Sequences

Sequence Number	Treatment Day 2	Treatment Day 4
Sequence A	HYC	HYC+DOX
Sequence B	HYC+DOX	HYC

Abbreviations: DOX = doxapram hydrochloride; HYC = hydrocodone bitartrate.

Each subject will be admitted on Day 1 and receive an oral dose of naltrexone according to [Section 4.1.1.2](#). Subjects will receive study drugs and scheduled assessments on Day 2 and Day 4 and be discharged on Day 5.

Premedications will be administered to all subjects according to [Section 4.1.1.2](#) prior to study treatment administration. Study treatment will be administered on Days 2 and 4, as specified in [Section 6.3](#). At least the first 24 hours of the 48-hour period between study treatment administration on Day 2 and Day 4 will be used for safety observation. Safety procedures and assessments will occur as specified in the SoA ([Section 1.3](#)).

4.1.1 Meals

Standard meals with a non-carbonated, non-xanthine, and non-grapefruit beverage will be provided to the subjects during their stay in the CRU.

Prior to receiving study drugs on Days 2 and 4, subjects will have a minimum 8 hour fast (no oral intake after midnight, except for clear liquids which may be consumed until 2 hours prior to study drug administration), and fast for no less than 4 hours after study drug administration.

Meals will be identical in composition for each period.

Except for study drug and immediately following dosing per protocol, no fluids will be allowed until 1-hour post-dose. Water will be provided *ad libitum* at all other post-dose times.

4.1.2 Premedication

- **Naltrexone:** prior to each study treatment administration on Day 2 and Day 4, oral naltrexone HCl (50 mg) will be administered twice: (i) once 12 ± 1 hours (night before) before study treatment administration and (ii) again on the treatment day, 1 hour $\pm$ 15 minutes prior to study treatment administration.

4.1.3 Rescue and/or Supplemental Medications

Management of medical emergencies is described in [Section 10.5.2](#).

The following rescue/supplemental medications will be available to use at the Investigator's medical discretion:

- **Naloxone:** Naloxone, a narcotic antagonist, will be readily available and will be administered intravenously or intranasally at the Investigator's medical discretion to reverse excessive CNS and respiratory depression if other interventions are deemed ineffective.
- **Sedatives:** to counteract possible sympathetic or CNS hyperexcitation, subjects may be treated with midazolam, propofol, or dexmedetomidine as deemed clinically appropriate by the Investigator.
- **Oxygen:** supplemental O₂ may be provided at the Investigator discretion.

Specific stopping criteria related to respiratory depression and sympathetic/CNS hyperexcitation are provided in [Section 7.2.1](#). Use of any rescue/supplemental medications will be appropriately documented.

4.2 Scientific Rationale for Study Design

4.2.1 Choice of Overall Study Design

This is a randomized, open label, crossover study in a single cohort of eight (8) healthy volunteers. This is a recognized and established Phase 1 study design that enables both a preliminary assessment of safety and tolerability of QEV-817 and an assessment of the magnitude of potential PK drug-drug interactions of oral DOX on HYC. The results of this study are intended to inform the design and dose selections for a subsequent dose-escalation study ([Section 4.3.1](#)).

Measures to ensure subject safety and management of medical emergencies are provided in [Section 10.5](#).

4.2.2 Choice of Study Population

Healthy volunteers were chosen to evaluate 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 because all subjects will be naltrexone-blocked and will therefore not be subject to any opioid pharmacology.

4.2.3 Choice of Population Size

A population size of eight (8) subjects is based on the reported variability in the plasma PK of oral HYC in human subjects, with the specific goal of statistically detecting a 50% increase in HYC plasma C_{max} values. Additional details are provided in [Section 9.3](#).

4.2.4 Choice of Primary Objectives and Endpoints

The primary objectives are (i) to assess the plasma pharmacokinetics of HYC with and without oral DOX and (ii) to assess the tolerability of 50 mg oral DOX in combination with 10 mg HYC. These objectives and corresponding endpoints are recognized and established for first-in-human (FIH) trials of novel combinations of medicinal products.

4.2.5 Choice of Duration of the Washout Period

A washout period of 48 hours between study drug administrations is implemented in this protocol.

The mean terminal half-life of HYC in plasma of recreational opioid users following administration of 60 mg in an oral solution similar to that proposed for the present study was found to be 5.4 hours ([Harris 2017](#)). Thus, a 48-hour washout would represent more than eight (8) half-lives.

A study of the oral PK of extended-release HYC in healthy volunteers found that the systemic exposure to the active metabolite hydromorphone was approximately 1% to 2% of the exposure

to the HYC parent in plasma, although the half-life of the metabolite was not reported in this study (Darwish 2017). When hydromorphone (4 mg) was itself administered in an immediate-release tablet in healthy subjects, the terminal half-life in plasma was reported to be 2.64 ± 0.88 hours (Vallner 1981), which is shorter than the half-life reported for the parent HYC. Thus, the low levels of hydromorphone metabolite anticipated following HYC administration can be presumed to be rapidly cleared (i.e., PK of the hydromorphone metabolite is formation rate limited in humans).

A 48-hour washout period is considered to be sufficient to prevent any clinically significant accumulation of HYC or its metabolites that could potentially affect subject testing on Day 4.

The terminal half-life of DOX following oral administration of an unoptimized oral formulation in healthy subjects was 7.5 hours, while that of the active 2-keto metabolite was reported to be slightly longer at 9.2 hours (Robson 1978). Although these values are expected to be shorter following administration in the optimized oral suspension proposed for this study. Therefore, a washout period of 48 hours between administrations would cover more than five (5) half-lives for both DOX and its active metabolite 2-keto-doxapram.

4.3 Justification of Doses and Posology

4.3.1 Hydrocodone Bitartrate

-----[REDACTED]----- a therapeutic dosage level of oral HYC of 10 mg has been selected to assess the plasma pharmacokinetics of HYC with and without oral DOX and to assess the tolerability of oral DOX in combination with HYC. This dosage level of HYC is approved for prescription use up to once every 6 hours in a number of immediate-release combination products marketed in the US.

4.3.2 Doxapram Hydrochloride

DOX is a respiratory stimulant, currently approved in the US for the intravenous treatment of respiratory depression caused by CNS-depressant drugs such as general anesthetics and opioids, with a maximum recommended dosage of 2 mg/kg up to every 5 minutes, not to exceed 3 grams in 24 hours (Dopram® Injection (doxapram hydrochloride, injection, USP) [Prescribing Information] 2004). Although not specifically approved for oral use, DOX has a long history of 'off-label' oral and nasogastric use in preterm infants with apnea of prematurity (Bairam 1991; Flint 2021; Poppe 2020; Romeo 1995). The PK-PD of oral DOX has been safely tested in healthy adult volunteers at dosage levels of 300 mg (Robson 1978) and at both 300 and 600 mg (Randall 1989). The oral bioavailability of DOX has been reported to be approximately 60% in adult human subjects (Robson 1978) and 74% in preterm infants (Flint 2021), and -----[REDACTED]----- in studies conducted by the Sponsor (QEV-817 IB).

As discussed in the QEV-817 IB, -----[REDACTED]----- the Sponsor has proposed a DOX starting dose of 50 mg for this study.

This study is intended to assess the magnitude of any potential PK drug-drug interactions of oral DOX as perpetrator, and oral HYC as victim drug. The Sponsor considers that the magnitude of any drug-drug interactions (DDIs) can be established in a single cohort using a fixed dose (50 mg) of DOX and a fixed, therapeutic dose (10 mg) of HYC.

4.4 End of Study Definition

The end of the study is defined as the date when the last subject has completed the final scheduled assessment or procedure shown in the appropriate SoA ([Section 1.3](#)) and is discharged from the CRU.

5.0 STUDY POPULATION

Subject eligibility must be verified prior to enrollment. Prospective approvals of protocol deviations to recruitment and enrollment criteria (also known as protocol waivers or exemptions) are not permitted as they could potentially jeopardize the scientific integrity of the study, regulatory acceptability, or subject safety.

Therefore, adherence to the criteria as specified in this protocol is essential.

5.1 Inclusion Criteria

Healthy volunteers are eligible to be included in the study only if all the following criteria apply:

General

- 1) Male or female aged 18–55 years, inclusive, on the day of screening.
- 2) Capable of understanding and providing written informed consent for participation in the study, including compliance with the requirements and restrictions as specified in the protocol.
- 3) Be available for the entire duration of the study.
- 4) Willing to abstain from alcohol and strenuous physical activity (i.e., strenuous, or unaccustomed weightlifting, running, bicycling, etc.) from 48 hours prior to study treatment administration until discharge from the clinical unit.
- 5) Have normal laboratory values, as defined in [Appendix 6](#), at screening. Abnormal laboratory values may be repeated at the discretion of the PI or designate
- 6) Absence of cardiac arrhythmias, as well as the following ECG criterion at screening:
 - Heart rate between 50 and 100 bpm, inclusive
 - QTc < 450 ms in males and QTc < 460 ms in females based on 12-lead ECG findings at screening
 - QRS interval $\leq$ 110 msec
 - PR interval $\leq$ 210 msec
- 7) Body weight $\geq$ 50 kg and body mass index (BMI) within the range of 19–32 kg/m² (inclusive).

Opioid Status

- 8) Has never used opioids for non-therapeutic purposes (i.e., for recreational effects). Subjects with a history of valid medical use under prescription must have not used an opioid for at least three (3) months prior to Day 1.

Reproductive Status and Contraception

(Details on contraception and barrier guidance are provided in [Section 10.4](#))

- 9) Women of childbearing potential (WOCBP), as defined in [Section 10.4](#):
 - a. All female subjects must have a negative serum pregnancy test within one (1) week AND a negative urine pregnancy test at admission on Day 1.
 - b. Must not be breastfeeding, lactating, or planning a pregnancy during the study and for at least 32 days (5 half-lives plus 30-days) after the last dose of study intervention.
 - c. WOCBP who are not exclusively in same-sex relationships must agree to remain abstinent (complete avoidance of heterosexual intercourse) or use adequate contraceptive methods, defined as use of a condom by the male partner combined with use of a highly effective method of contraception (defined in [Section 10.4](#)) by the female partner, during the treatment period and for at least 32 days (5 half-lives plus 30-days) after the last dose of study intervention.
- 10) Women of non-childbearing potential (WONCBP), as defined in as defined in [Section 10.4](#), and female participants with vasectomized male partners:
 - a. Must have a negative serum pregnancy test within one (1) week AND a negative urine pregnancy test at admission on Day 1.
 - b. WONCBP must agree to remain abstinent (complete avoidance of intercourse) or the male partners of WONCBP participants must wear a condom to protect against the transfer of study intervention through bodily fluids during the treatment period and for at least 48 hours (>5 half-lives) after the last dose of study intervention.
- 11) Postmenopausal females must have a documented serum follicle-stimulating hormone (FSH) and estradiol level consistent with menopause as per reference laboratory ranges at screening to confirm menopause. Additional details are provided in [Section 10.4](#).
- 12) Male participants:
 - a. Male participants must inform their female sexual partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner.
 - b. Male participants with female sexual partners who are WOCBP must agree to remain abstinent (complete avoidance of heterosexual intercourse) or use adequate contraceptive methods, defined as use of a condom by the male partner combined with use of a highly effective method of contraception (defined in [Section 10.4](#)) by

the female partner, during the treatment period and for at least 92 days (5 half-lives + 90-day spermatogenesis cycle) after the last dose of study intervention.

- c. Male participants must not donate sperm for at least 92 days (5 half-lives + 90-day spermatogenesis cycle) after the last dose of study intervention.
- d. Male participants in same-sex relationships or in relationships with WONCBP, as defined in [Section 10.4](#), must agree to remain abstinent (complete avoidance of intercourse) or use a condom to prevent exposure of the partner to study intervention through ejaculate/seminal fluid during the treatment period and for at least 48 hours (>5 half-lives) after the last dose of study intervention.

5.2 Exclusion Criteria

Healthy volunteers who meet any of the following exclusion criteria will be excluded from participation in the study:

Medical History and Clinical Laboratory

- 1) Female subject who is pregnant or lactating.
- 2) Have any of the following vital sign abnormalities:
 - Systolic pressure >140 and/or <90 mmHg
 - Diastolic pressure >90 and /or <50 mmHg
 - Heart rate >100 and/or <50 bpm
 - Respiratory rate >20 and/or <12 breaths per minute
- 3) Recreational opioid user who has used opioids for non-therapeutic purposes (i.e., for psychoactive effects).
- 4) Physically dependent on any illicit or prescription opioid, and/or currently participating in a treatment program for individuals with opioid dependence.
- 5) Known allergy or history of significant adverse reaction to hydrocodone (HYC) or its metabolites, other opioids, or related compounds, doxapram hydrochloride (DOX), naltrexone, naloxone, or to any of the excipients in QEV-817.
- 6) History of or currently has hypoventilation syndrome or sleep apnea and is on non-invasive ventilation (e.g., CPAP).
- 7) Clinically meaningful infection/injury/illness within one month prior to screening.

- 8) Active malignancy (excluding squamous or basal cell carcinoma of the skin) within 5 years of screening.
- 9) Positive serology for hepatitis B virus (HBV), hepatitis C virus (HCV), or human immunodeficiency virus (HIV) at Screening
- 10) Subjects with hepatic impairment as defined by screening alanine transaminase (ALT), aspartate transaminase (AST) or total bilirubin $>3\times$ upper limit of normal (ULN).
- 11) Subjects with renal impairment as defined by screening estimated creatinine clearance/eGFR using the CKD-EPI equation is <60 mL/min/1.73 m².
- 12) Donation of blood (>450 mL) or significant blood loss within the last 6 months.
- 13) Current (or recent history of) psychiatric illness or mental impairment.
- 14) Clinically meaningful current (or history of) unstable chronic disease; medical abnormality; or significant cardiovascular (including significant cardiovascular impairment, uncompensated heart failure, severe coronary artery disease, severe hypertension), endocrine, gastrointestinal, neurological disorder (including cognitive disorders); or metabolic disease.
- 15) Currently active (or history of) epilepsy, seizure disorder, serious head injury, cerebral vascular accident, or cerebral edema.
- 16) Current treatment with monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, sympathomimetic drugs, neuromuscular blocking agents, narcotics, antihistamines, antipsychotics, antianxiety agents, or other CNS depressants.
- 17) Conditions the Investigator believes would interfere with the ability to provide informed consent or comply with study instructions, or that might confound the interpretation of the study results or put the subject at undue risk.
- 18) History of a medical condition that, in the opinion of the Investigator, would compromise the subject's ability to swallow, absorb, metabolize, or excrete test product, including (but not limited to) intractable nausea and/or vomiting and/or severe gastrointestinal narrowing (pathologic or iatrogenic).
- 19) Use of any prescription or OTC medications including food supplements and herbal medications (e.g., St. John's wort), with the exception of contraceptive medications or a daily multivitamin, within fourteen (14) days prior to study treatment administration. Use of CYP3A4 inhibitors or inducers is prohibited within 28 days prior to the first treatment and throughout the treatment and follow-up periods.

- 20) Any condition or finding that in the Investigators opinion would put the subject or study conduct at risk if the subject were to participate in the study.

Lifestyle

- 21) A positive urine drug, cotinine, or alcohol test at screening, or at Admission on Day 1, excluding tetrahydrocannabinol (THC) or cannabinoid metabolites.
- 22) Smokers or use of tobacco-containing products within 6 weeks of study drug administration.
- 23) Use of grapefruit-containing foods or beverages or Seville orange-containing foods or beverages is prohibited within 14 days prior to the first treatment and throughout the treatment and follow-up periods.

5.3 Subject Enrollment

Subject eligibility must be verified prior to enrollment. Following confirmation of eligibility, subjects will be randomly assigned to one of two treatment sequences. Each eligible subject will be assigned with a unique randomization number in the order in which they are enrolled in the study. The randomization number will be assigned according to a randomization code list generated by the study site. Once the randomization number is assigned, it cannot be reassigned, even if the subject is deemed ineligible or withdraws consent prior to study treatment.

5.4 Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE) that occurs after completion of the informed consent form (ICF).

5.5 Subject Replacement

Subjects who withdraw or are removed from the study without experiencing an AE may be replaced at the discretion of the Sponsor. Replacement subjects will not be randomized but will be assigned to the same study treatment sequence as the replaced subject.

6.0 STUDY TREATMENT

6.1 Study Treatment Administered

Study interventions are described in Table 4. For complete information regarding reconstitution of the drug products to the clinical trial material, QEV-817-S, and administration of study intervention refer to the Pharmacy Manual.

Table 4: Protocol QEV-817-101: Study Interventions

Intervention Name	QEV-817-S	HYC-S
Alias	HYC+DOX	HYC
Type	Investigational product	Control
Dose Formulation	Oral Suspension	Oral Suspension
Unit Dose Strength(s)	-----[REDACTED]-----	-----[REDACTED]-----
Dosage Level(s)	10 mg HYC+50 mg DOX	10 mg HYC
Route of Administration	Oral	Oral
Use	Experimental	Experimental
Sourcing	Supplied as a powder for oral suspension by Frontage Laboratories and reconstituted at the clinical site.	Supplied as a powder for oral suspension by Frontage Laboratories and reconstituted at the clinical site.
Storage	Store refrigerated (2°C to 8°C), not to exceed 24 hours.	Store refrigerated (2°C to 8°C), not to exceed 24 hours.
Packaging and Labeling	-----[REDACTED]-----	-----[REDACTED]-----
Reconstitution and Handling	Reconstitution carried out at the clinical trial site per the Pharmacy Manual.	Reconstitution carried out at the clinical trial site per the Pharmacy Manual.

Abbreviations: HYC = hydrocodone bitartrate; DOX = doxapram hydrochloride.

6.2 Preparation/Handling/Storage/Accountability

-----[REDACTED]-----

Only subjects enrolled in the study may receive study drug, which may only be supplied or administered by authorized site staff. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the

labeled storage conditions/manufacturer's instructions, with access limited to the pharmacist or designee.

The pharmacist or designee is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). The pharmacist or designee will maintain a record of all study drug received and dispensed.

Additional guidance and information for the final disposition of unused study drug are provided in the Pharmacy Manual.

6.3 Assignment to Study Intervention and Study Treatment Administration

Prior to study treatment administration on Day 2, subjects will be assigned a unique randomization number in ascending numerical order at the study site. The randomization number encodes the participant's assignment to one of the treatment sequences (Table 3) of the study, according to the randomization schedule generated prior to the study by the study site. Each subject will be dispensed study treatment, labeled with the participant's unique randomization number, throughout the study.

Study treatments will be administered after a minimum 8 hour fast (no oral intake after midnight, except for clear liquids which may be consumed until 2 hours prior to study drug administration). All subjects will receive a 50 mg dose of oral naltrexone HCl approximately 1 hour prior to study drug administration. All subjects will receive a single oral dose of 10 mg HYC either alone or combined with a 50 mg dose of DOX in randomized sequence (Table 3). -----
[REDACTED]----- Subjects will be required to consume the entire study treatment suspension within 10 minutes.

All subjects will receive two treatments as specified in Table 3, with a 48-hour washout between treatments.

6.4 Treatment Compliance

The study drug will be administered and recorded only by authorized study personnel at the study site. The dose of study drug and subject identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study drug. The date and time of each dose administered will be recorded in the source documentation. The subject will be confined in the CRU for safety monitoring and other study procedures. Subject compliance monitoring is therefore ensured.

6.5 Dose Modifications

Not applicable. Dose modifications are not permitted.

6.6 Access to Study Intervention After End of Study

Administration of study intervention(s) under this protocol will be completed per protocol. No further treatment of study intervention(s) is permitted.

6.7 Treatment of Overdose

For this study, any dose of study intervention greater than the specified dose is considered overdose. Specific treatments for signs and symptoms of HYC and/or DOX overdose are provided in [Section 4.1.1.3](#) and [Section 10.5](#).

In the event of an accidental overdose, the Investigator should do the following:

- Treat signs and symptoms of overdose according to [Section 4.1.1.3](#) and/or [Section 10.5](#).
- Contact the Sponsor/Medical Monitor immediately.
- In consultation with the Sponsor/Medical Monitor, determine whether additional steps should be taken.
- Closely monitor the subject for any AEs or SAEs and treat any AEs with appropriate supportive care.
- Document the quantity of the excess dose.

Overdoses without signs or symptoms do not need to be recorded as AEs; any AEs associated with the overdose should be reported on relevant AE/SAE sections in the eCRF. Overdoses and medication errors will be documented as protocol deviations.

6.8 Concomitant Medications and Procedures

A concomitant medication is any medicinal product or substance administered between signing the ICF and the 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 medication or vaccine the subject is receiving at the time of enrollment or receives during the study must be recorded along with the reason for use, start and end dates, dose, and frequency.

6.8.1 Allowed Concomitant Medications and Procedures

Allowed concomitant medications include the following:

- Contraceptive medications.

- Daily multivitamin.

Any concomitant medication deemed necessary for the welfare of the subject during the study may be given at the discretion of the Investigator. It is the responsibility of the Investigator to ensure that details regarding the medication are recorded in full in the eCRF. Use of all concomitant medications during study participation will be recorded in the subject's eCRF. The Medical Monitor should be contacted if there are any questions regarding prior or concomitant therapy.

6.8.2 Prohibited Concomitant Medications and Procedures

All prescription or over-the-counter (OTC) medications, including food supplements and herbal medications (e.g., St. John's wort) are prohibited unless specified as allowed in [Section 6.8.1](#).

Grapefruit-containing foods or beverages or Seville orange-containing foods or beverages are prohibited within 14 days prior to the first treatment and throughout the treatment and follow-up periods.

Use of CYP3A4 inhibitors or inducers is prohibited within 28 days prior to the first treatment and throughout the treatment and follow-up periods.

Any prescription medication deemed by the Investigator to confound interpretation of study results or presents a safety concern is prohibited.

A positive urine drug or alcohol test ([Section 10.2](#)) at screening or upon admission on Day 1 will exclude the subject from study participation (except for cannabinoids).

6.8.3 Rescue Medication or Supportive Therapy for Adverse Events

Refer to [Section 4.1.1.3](#) and [Section 10.5](#).

7.0 DISCONTINUATION OF STUDY TREATMENT AND SUBJECT WITHDRAWAL

7.1 Subject Withdrawal and/or Discontinuation of Study Intervention

If a subject who does not meet enrollment criteria is inadvertently enrolled, that subject should be withdrawn from the study and the Sponsor, or its designee, must be contacted immediately. All subjects are free to withdraw from participating in this study at any time for any reason, specified or unspecified, and without prejudice. No constraints will be placed on ordinary subject management. If a subject intends to withdraw consent, the site should make every effort to complete the ET Visit per the SoA.

Discontinuation of study intervention will be considered, in consultation with the Sponsor, or designee, for any of the following reasons:

- The subject experiences an intolerable AE or SAE.
- The subject withdraws consent.
- The subject is unwilling or unable to comply with the protocol.
- The subject dies.
- At the discretion of the Investigator or Sponsor.
- Investigator decision that it is not in the best medical interest of the subject to continue participation in the investigation.
- The Sponsor prematurely terminates the study.

Subjects who discontinue from study intervention should complete all safety follow-up activities, as outlined in the SoA ([Section 1.3](#)), to the best extent possible. AEs will be followed as described in [Section 8.3](#).

Subject withdrawals will be documented clearly on the source documents and applicable case report forms (CRFs).

Notification of subject withdrawals will be made to the Sponsor, or designee.

7.2 Specific Subject Stopping Criteria

7.2.1 Sympathetic/CNS Hyperexcitation

Subjects who experience clinically significant symptoms of sympathetic or CNS hyperexcitation will be treated with midazolam, propofol, or dexmedetomidine as deemed clinically appropriate by the Investigator and will be discontinued from study treatment. Possible behavioral manifestations could include excessive agitation, uncooperative behavior, or panic attack.

Cardiopulmonary manifestations of excessive sympathetic tone are addressed in the [Sections](#) that follow.

7.2.2 Excessive Opioid Narcosis/Respiratory Depression

Although unlikely (as opioid effects will be blocked with naltrexone), any subject that exhibits sustained blood oxygen saturation (SpO_2) < 90%, which does not respond to supplemental oxygen will receive opioid reversal via nasal or intravenous naloxone (per flow scheme in [Section 10.5](#)) and be discontinued from study treatment.

7.2.3 Cardiac Safety

Subjects with the following ECG findings will be immediately discontinued from study treatment:

- Any ventricular fibrillation (see also Trial Stopping Rules in [Section 7.4](#)),
- Grade 3 or higher ventricular arrhythmia (bradycardia or tachycardia; [Table 5](#)).

7.2.4 Vital Signs

Subjects with the following vital sign findings (confirmed upon repeat testing) per [Table 5](#) will be immediately discontinued from study treatment:

- Grade 3 or higher fever
- Grade 3 or higher systolic hypotension
- Grade 3 or higher systolic hypertension
- Grade 3 or higher tachypnea
- Grade 3 or higher bradypnea

Table 5: Protocol QEV-817-101: Clinical Vital Signs Abnormalities

Vital Sign *	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Fever (°C) **	38.0 – 38.4	38.5 – 38.9	39.0 – 40	>40
(°F) **	100.4 – 101.1	101.2 – 102.0	102.1 – 104	>104
Tachycardia - beats per minute	101 – 115	116 – 130	>130	ER visit or hospitalization for arrhythmia
Bradycardia - beats per minute***	50 – 54	45 – 49	<45	ER visit or hospitalization for arrhythmia
Hypertension (systolic) - mm Hg	141 – 150	151 – 155	>155	ER visit or hospitalization for malignant hypertension

Hypertension (diastolic) - mm Hg	91 – 95	96 – 100	>100	ER visit or hospitalization for malignant hypertension
Hypotension (systolic) – mm Hg	85 – 89	80 – 84	< 80	ER visit or hospitalization for hypotensive shock
Respiratory Rate (tachypnea) – breaths per minute	17 – 20	21 – 25	>25	Intubation
Respiratory Rate (bradypnea) – breaths per minute	8 – 10	5 – 7	<5	Intubation

* Subject should be at rest for all vital sign measurements.

** Oral temperature; no recent hot or cold beverages or smoking.

*** When baseline resting heart rate is between 60 – 100 beats per minute. Use clinical judgement when characterizing bradycardia among some healthy subject populations, for example, conditioned athletes.

Source: adapted from FDA Guidance for Industry: *Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials* (2007).

7.2.5 Other Findings

Examples of other findings that would lead to immediate subject discontinuation from study treatment include the following:

- Clinically meaningful infection, injury, or illness, as determined by the Investigator;
- Headache severe enough to require repeated use of non-narcotic pain reliever >24 hours or otherwise results in interference of activity; and/or
- Any other adverse finding or event that is considered serious enough by the Investigator to warrant subject discontinuation from the study.

7.3 Lost to Follow-up

Subjects who do not return for a scheduled visit (missed visit) and cannot be contacted, may be considered lost to follow-up. The site will attempt to contact the subject through a minimum of two telephone calls. If the subject still cannot be contacted, the site will send a certified letter to the last known address of the subject. If no contact is made by the subject, the site will consider the subject lost to follow-up. All follow-up attempts will be documented and kept with the subject's source documentation, and the applicable CRFs will be completed.

7.4 Trial Stopping Rules

The study will be stopped by the Sponsor for any of the following reasons:

- AEs or SAEs indicative of seizure in any one or more subjects.
- AEs or SAEs indicative of ventricular fibrillation in any one or more subjects.

8.0 STUDY ASSESSMENTS AND PROCEDURES

Written informed consent must be provided before any study-related procedures/assessments are performed. Subjects will have the opportunity to have any questions answered prior to signing the ICF. The Investigator or designee must address all questions raised by the subject and will also sign the ICF.

Planned timepoints for all assessments and procedures are provided in the SoA ([Section 1.3](#)).

8.1 General/Pharmacokinetics Study Assessments

8.1.1 Demographics and Medical History

Demographic data will include age, sex, BMI, and ethnic origin (also referred to as self-reported race and ethnicity in some regions).

Medical history includes the following:

- History of all known allergies.
- All prescription medications used by the subject regularly or within 30 days preceding Day 1.
- Current medications, including OTC preparations.
- History of substance abuse and recreational drug use.
- History of prescription opioid use for valid medical reasons in last 5 years.
- History of depression, anxiety, mental illness, emotional problems, use of psychiatric medications, and previous psychotherapy.
- History of ongoing medical illnesses.
- Surgical procedures and results.
- History of clinically significant diseases.
- History of blood donation in the previous 6 months.
- Organ or stem cell transplants.
- Reproductive status.

The conditions that are pre-existing and still ongoing at the time of informed consent will be recorded and monitored throughout the course of the subjects' participation in the study.

8.1.2 Physical Examination

The screening physical examination will consist of a review of all body systems for the purpose of assessing any potential underlying diseases or irregularities that would exclude participation in

the study. A symptom-directed physical exam may be conducted at subsequent visits when needed.

Complete physical examination includes the following:

- Height.
- Weight.
- Vital signs ([Section 8.2.4](#)).
- Review of systems excluding genitourinary examination. Systems/organs to examine include 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.

8.1.3 Urine Drug and Alcohol Screen

A urine sample for drug and alcohol testing will be obtained at the screening visit and upon admission to the CRU on Day 1, as specified in the SoA ([Section 1.3](#)). The list of analytes to be tested is provided in [Section 10.2](#). A positive urine drug or alcohol test at screening is exclusionary ([Section 5.2](#)), except for tetrahydrocannabinol (THC) or cannabinoid metabolites.

8.1.4 Pharmacokinetics

A peripheral intravenous catheter will be established for repeated blood sampling at the timepoints specified in the SoA ([Section 1.3](#)). If the catheter is not tolerated or becomes non-functional, venipuncture may also be utilized to collect blood PK samples.

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.

Sample collection, processing, and shipping will be performed according to the Laboratory Manual. For the sample delivery, the samples will be frozen and sent by courier to the bioanalytical facility. The bioanalytical laboratory will be notified that a shipment is planned at least 1 day prior to the shipment.

After the collected blood samples are analyzed for study drug concentrations, any leftover samples may be used for analysis and testing for potential research on additional metabolites or other indicators of subject outcome. Not all potentially beneficial future research can be known at any one time, as the need for future research is determined by ongoing developments in the

field. Leftover blood samples may be stored at least until the study results have been reported and will be destroyed no later than 2 years after the final clinical study report.

8.1.5 Richmond Anxiety Sedation Scale (RASS)

The Investigator or designee will complete the Richmond Agitation Sedation Scale (RASS) at the timepoints specified in the SoA ([Section 1.3](#)). Responses range from -5 (Unarousable) to +4 (Combative).

8.2 Safety Assessments

Additional safety parameters may be added at the discretion of the Investigator on the basis of the observations from clinical findings in any subject treated in this study. Safety assessments will be conducted as shown in the SoA ([Section 1.3](#)).

The Investigator will determine whether any safety related observations are clinically significant or not clinically significant. Clinically significant is defined as any variation in results that has medical relevance and may result in an alteration in medical care (e.g., active observation, diagnostic measures, or therapeutic measures). If a clinically significant change from the screening values is noted, the clinically significant value and reason for clinical significance will be documented in the subjects' source documents and on the AE page of the subject's eCRF. The Investigator will continue to monitor the subject with additional assessments until the value has reached the reference range or the value at screening, or the Investigator determines that follow-up is no longer medically necessary.

Sample collection, processing, and shipping will be performed according to the Laboratory Manual.

8.2.1 Pregnancy Testing

A serum pregnancy test will be obtained within one week prior to Day 1 at Screening in WOCBP (defined in [Section 10.4.1](#)). A urine pregnancy test will be obtained upon admission to the CRU on Day 1 in WOCBP.

8.2.2 Chemistry/Hematology/Urinalysis

Chemistry/hematology/urinalysis will be obtained at screening and approximately 24 hours ($\pm$ 1 hour) after each study drug administration (i.e. on study Day 3 and prior to discharge on study Day 5) as specified in the SoA ([Section 1.3](#)). Subjects will be fasted at least 8 hours prior to laboratory tests. Specific tests are listed in [Section 10.2](#).

Local laboratories will be utilized for all standard laboratory assessments.

An Investigator must sign and date each of the laboratory reports to document review and determine whether abnormal values are clinically significant or not clinically significant and may

require intervention or lead to study discontinuation. Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis), including those that worsen from baseline screening, determined to be clinically significant in the medical and scientific judgment of the Investigator are to be recorded as AEs.

8.2.2.1 Reporting and Evaluation of Laboratory Test Results

Adverse events will be collected from the time of dosing; therefore, the screening laboratory results are considered baseline. All laboratory test results collected after study drug administration must be reviewed for clinical significance by the Investigator. Laboratory test results outside the normal range (hematology, chemistry, urinalysis) that worsen in severity grade (mild, moderate, severe) from baseline and are deemed clinically significant by the Investigator should be reported as AEs. A new laboratory abnormality resulting in study drug interruption, dose reduction, treatment discontinuation, intervention, is symptomatic, requires treatment or otherwise has an impact on the subject should be reported as an AE, unless it is part of a clinical diagnosis already reported as an AE.

All laboratory values outside the normal range are to be evaluated before the next dose of study drug.

8.2.2.2 Repeat Testing

Repeat testing of any clinically significant laboratory test will be performed until the value returns to within the normal range or baseline level, clinically stabilizes, or the subject is lost to follow-up.

8.2.3 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 ([Section 1.3](#)). 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).

8.2.4 Vital Signs

Includes systolic and diastolic blood pressure, pulse rate, respiratory rate, and blood oxygen saturation (pulse oximetry). Subjects must 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. Vital signs will be measured at the time points indicated

in the SoA ([Section 1.3](#)). AEs related to vital signs will be graded using the scale provided in [Table 5](#).

8.2.5 Body Temperature

Body temperature will be assessed orally at screening and on Days 2, 4, and 5 at the timepoints specified in the SoA ([Section 1.3](#)).

8.3 Adverse Events, Serious Adverse Events, and Other Safety Reporting

The definitions of AEs and SAEs; the methods of recording, evaluating, and assessing causality of AEs and SAEs; and the procedures for completing and transmitting SAE reports are provided in [Section 10.3](#).

Adverse events will be graded for seriousness, severity (mild, moderate, severe), and relationship to study treatment.

After obtaining informed consent, each subject must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

8.3.1 Time Period and Frequency for Collecting AE and SAE Information

All AEs and SAEs will be monitored and recorded from the time of admission to the CRU until discharge from the CRU. All study- or treatment-related SAEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up ([Section 8.3.3](#)).

Throughout the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

8.3.2 Method of Detecting AEs and SAEs

Adverse events may be spontaneously reported by the subject, obtained through non-leading questioning, or noted during examination of a subject.

When recording an AE, a diagnosis is always preferable; however, in the absence of a diagnosis, the Investigator should record each sign and symptom as an individual AE.

Medical or surgical procedures (e.g., cardiac ablation) should not be recorded as AEs. Rather, the condition for which the procedure was performed should be recorded.

Adverse events will be recorded from the time informed consent ([Section 10.1.3](#)) is obtained through the end of the study. The data will be recorded on the appropriate CRF, regardless of whether they are thought to be associated with the study or study treatment.

Investigators are not obligated to actively seek SAE information from subjects that complete the study but are encouraged to notify the Sponsor or designee of any SAE occurring at any time after a subject has discontinued or completed the study that they judge may be reasonably related to study treatment or study participation.

8.3.3 Assessment of Causality for AEs and SAEs

Every effort should be made by the investigator to try to explain each AE and assess its relationship, if any, to the study drug or to protocol required pre-medication (ie. naltrexone). The temporal relationship of the event to study drug administration should be considered in the causality assessment (i.e. if the event starts soon after study drug administration).

Causality should be assessed using the following categories:

Unrelated:	Clinical event with an incompatible time relationship to study drug administration, and that could be explained by underlying disease or other drugs or chemicals or is incontrovertibly not related to the study drug.
Possibly related:	Clinical event with a reasonable time relationship to study drug administration, and that is unlikely to be attributed to concurrent disease or other drugs or chemicals.
Related:	Clinical event with plausible time relationship to study drug administration and that cannot be explained by concurrent disease or other drugs or chemicals.

The degree of certainty with which an AE is attributed to study drug administration (or alternative causes, e.g. natural history of the underlying disease, concomitant therapy) will be determined by how well the experience can be understood in terms of one or more of the following:

- Known pharmacology of the study drug.
- Reactions of a similar nature have been previously observed with the study drug or this class of drug.
- The experience being related by time to study drug administration, terminating with study drug withdrawal or recurring on re-challenge.
- Alternative cause.

8.3.4 Follow-up of AEs and SAEs

All related SAEs must be followed until resolution, until the condition stabilizes, until the event is otherwise explained, or the subject is lost to follow-up. The Investigator is responsible to ensure that follow-up includes any supplemental investigations as may be indicated to elucidate as completely as practical the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, relevant hospital

records (i.e., discharge summary), or consultation with other health care professionals, ensuring that all subject identifiers have been redacted from supportive documentation prior to submission.

The Sponsor or designee may request that the Investigator perform or arrange for the conduct of supplemental measurements and/or evaluations. If a subject dies during participation in the study or during a recognized follow-up period, the Sponsor or designee should be provided with a copy of any postmortem findings, including histopathology.

New or updated information obtained during SAE follow-up should be recorded in the original/existing form(s); updates should be made to the relevant data in the Electronic Data Collection (EDC). If EDC is not available, then new or updated information should be recorded on a new paper SAE form; the original or prior paper SAE forms must not be re-used or altered. By signing the SAE form, the Investigator or designee attests to the accuracy and completeness of the data and that he/she has reviewed the report being submitted and approves it. If a paper form is used, the same information is to be captured in the EDC when EDC becomes available.

8.3.5 Regulatory Reporting Requirements for SAEs

Any SAE experienced by the subject between the time of admission to the CRU through end-of-study must be recorded on an SAE form, regardless of the severity of the event or its relationship to the study treatment. Once the Investigator determines that the event meets the protocol definition of an SAE, the SAE must be reported to the Sponsor, or designee, within 24 hours.

Prompt notification of an SAE by the Investigator to the Sponsor is essential to meet the legal obligations and ethical responsibilities regarding the safety of subjects and the safety of a study intervention under clinical investigation.

The Investigator is obligated to obtain supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the event as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The SAE Report Form must be printed and signed, and emailed to:

Name	John H. Hsu, MD (Chief Medical Officer of Quivive Pharma, Inc.)
Telephone	-----[REDACTED]-----
Email	-----[REDACTED]-----

The SAE Report Form must be retained in the site records. Follow-up information will be reported in the same method as above.

Reporting of a SAE requires the following:

- Completion of the SAE Report Form details in the EDC, or if the EDC is not available, transmission of the paper SAE Report Form to the Sponsor or designee, via email as noted above. The SAE event is to be reported within 24 hours of the Investigator's knowledge of the event. If paper submission is used, the same information is to be entered into the EDC when EDC becomes available.
- Reporting of additional follow-up information for previously reported SAEs should follow the same reporting timeframe and procedures as initial reports. New or updated information should be made to the relevant data in the EDC. If EDC is not available, new or updated information should be recorded on a new paper SAE form; the original or prior paper SAE forms must not be re-used or altered.
- Accompanying documentation, such as laboratory data, concomitant medication records, hospital records etc., should be redacted and transmitted to the Sponsor or designee. In addition, the corresponding AE in the AE CRF (as applicable) should be updated to ensure all data points documented in the AE CRF are aligned with the matching data points on the SAE Report Form.

The Sponsor has a legal responsibility to notify health authorities about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the local regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

An Investigator who receives an Investigator Safety Report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, as appropriate according to local requirements.

Investigator Safety Reports must be prepared for suspected unexpected serious adverse reactions (SUSARs) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.

8.3.6 Pregnancy

The Investigator must report a pregnancy occurring in a female subject to the Sponsor or designee within 24 hours of the study site staff becoming aware of the pregnancy. The Investigator or study site staff must also follow the pregnancy until the outcome is known and submit the outcome as follow-up within 24 hours of notification of outcome. Follow-up Pregnancy Forms may be submitted as required for additional information obtained. Although pregnancy occurring in a clinical study is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy, for medical reasons, will be recorded as an AE or SAE and followed as such. Pregnancies in partners of male study subjects will similarly be monitored for the full duration of the pregnancy and/or followed through a definitive outcome

(i.e., birth, or spontaneous or elective abortion), as described in [Section 10.4.2](#). Pregnancy reporting must be submitted via email to:

Name	John H. Hsu, MD (Chief Medical Officer of Quivive Pharma, Inc.)
Telephone	-----[REDACTED]-----
Email	-----[REDACTED]-----

8.3.7 Death Events

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to the Sponsor, or designee. If cause of death is not available within the 24-hour reporting period, “death” must be reported as SAE term to meet timelines and the cause of death actively queried and submitted as a follow-up report.

9.0 STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be written and approved prior to database lock.

9.1 Statistical Hypothesis

No formal statistical hypothesis testing will be performed.

9.2 Definition of Enrollment

“Enrolled” means a subject's agreement to participate in this clinical study following completion of the screening and informed consent processes. Potential subjects who are screened for the purpose of determining eligibility for the study, but who do not participate in the study, are not considered enrolled.

9.3 Sample Size Determination

To support the PK comparison of HYC with and without co-administration with DOX, a sample size of eight (8) subjects was determined by statistical analysis of the minimum detectable effect (MDE) for a clinical PK interaction for HYC. This was based on the reported variability in the plasma PK of oral HYC in human subjects using natural log transformed values of the three (3) primary pharmacokinetic (PK) parameters: C_{max} , $AUC_{(0-t)}$, and $AUC_{(inf)}$. C_{max} was found to have the highest variability of the three (3) primary pharmacokinetic (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. (Report QEV817-CL-001)

9.4 Analysis Populations

For the purposes of analysis, the following populations are defined:

Analysis Population	Definition
Safety	Includes all subjects who received at least one dose of study drug. This is the primary population for exposure and safety analyses.
Pharmacokinetic	Includes 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.
Pharmacodynamic	Includes all randomized subjects who received study drug and have evaluable pharmacodynamic (PD) data. This is the primary population for PD analysis.

9.5 Statistical Analyses

9.5.1 General Considerations

Data listings will be provided for safety, PK and pharmacodynamic (PD) data and parameters. Summary statistics will be provided for safety data, PD, and PK data and parameters by dose level and/or treatment. For continuous variables, descriptive statistics (n, mean, standard deviation (SD), median, minimum, and maximum) will be provided. For categorical variables, subject counts and percentages will be provided.

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.

Subject disposition will be summarized 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 provided in a listing with reasons for deviation and date of occurrence. Any exclusion of subjects from analysis populations, and how these exclusions affect data analysis, will be addressed in the clinical study report.

Missing Data

There will be no imputation for missing safety data. Other missing data will simply be noted as missing on appropriate tables/listings.

9.5.2 Safety and Tolerability

Safety data will be summarized through appropriate data tabulations. For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges.

All out-of-range and clinically significant laboratory results will be identified in subject data listings. The number and percentage of subjects in each dose group with normal and abnormal physical examination results will be presented for evaluations at baseline and final visit.

All AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) v28.0 or higher. Each AE will be counted only once, and the most severe will be counted in each subject and in each preferred term or system organ class category for the analyses of safety. Summaries will be presented for all AEs (overall and by severity), AEs determined by the Investigator to be related to DOX+HYC or HYC (i.e., reasonable possibility, defined as related

or with missing relationship; overall and by severity), SAEs, and AEs causing withdrawal from the study. Subject listings of SAEs and AEs leading to withdrawal will be presented.

Changes in vital signs and liver function test data will be summarized descriptively by time point. AEs related to vital signs will be graded using the scale provided in Table 5. Changes in ECG measurement data will be summarized descriptively by time point. All values will be compared in the clinic and assessed by the Investigator, with prespecified boundaries to identify potentially clinically significant values, and such values will be listed.

Physical examination findings will be listed by subject and visit. Laboratory data will be summarized by the type of laboratory test and chronological time point. Abnormal findings in laboratory data will be listed with a flag for low/high/abnormal based on normal ranges provided by the clinical laboratory.

9.5.3 Pharmacokinetics

9.5.3.1 Plasma Concentration Data

Plasma concentrations of HYC, DOX, and their respective metabolites will be listed by subject, treatment, and nominal sampling times. Plasma concentrations will be summarized by treatment and nominal sampling time using the PK Analysis Population and the following descriptive statistics: number of observations (n), arithmetic mean, arithmetic SD, arithmetic coefficient of variation (CV), median, minimum, and maximum.

Figures of individual plasma concentration versus actual time profiles for HYC and metabolite hydromorphone will be produced on semi-log scale. Mean plasma concentration versus nominal time curves will be plotted for all treatments together using the PK Analysis Population on semi-log scale.

9.5.3.2 Plasma Pharmacokinetic Parameters

Plasma PK parameters for HYC, DOX, and their respective metabolites hydromorphone and 2-keto-doxapram, will be derived by noncompartmental methods. From the plasma concentration-time data, the following plasma PK parameters will be determined, as data permit:

AUC_{0-t}	Area under the plasma concentration-time curve to the time of last quantifiable concentration, calculated by the linear trapezoidal linear interpolation method
$AUC_{0-\infty}$	Area under the plasma concentration-time curve extrapolated to infinity, calculated as $AUC_{0-t} + C_t/\lambda_z$, 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}	Apparent elimination rate constant
$t_{1/2}$	Elimination half-life, calculated as $0.693/\lambda_z$

AUC _{0-t}	Area under the plasma concentration-time curve to the time of last quantifiable concentration, calculated by the linear trapezoidal linear interpolation method
CL/F	Apparent total 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)

Individual subject plasma PK parameter data will be tabulated. Pharmacokinetic parameters for DOX, HYC and metabolites will be tabulated by treatment within cohort. Data from subjects prematurely ending participation in the study may be excluded from the PK. The details of PK analysis will be provided in the SAP.

Pharmacokinetic parameters will be listed by subject and treatment and summarized by treatment using the PK Analysis Population and the following summary statistics: n, arithmetic mean, SD, CV, minimum, median, and maximum. Geometric mean and geometric CV will also be presented for all PK parameters except T_{max}.

In addition, formal statistical analysis will be performed on the PK parameters C_{max}, AUC_(0-t) and AUC_(0-∞) for HYC to assess the impact of DOX coadministration on the PK of HYC. Natural log-transformed PK parameters C_{max}, AUC_{0-t}, and AUC_{0-∞} 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 adjusted geometric mean ratios and 90% confidence intervals for each comparison will be tabulated for C_{max}, AUC_(0-t) and AUC_(0-∞), where the geometric mean ratios are defined as “HYC+DOX / HYC”.

For additional information, PK comparisons for HYC metabolite hydromorphone may also be conducted between treatment groups using descriptive statistics, where deemed appropriate. Formal statistical analysis of metabolite hydromorphone may be performed where data allow.

9.5.4 Other Analyses

Summary statistical analyses will be provided for demographics, medical history, physical examination, and other variables at baseline.

9.5.5 Interim Analyses

A formal interim analysis is not planned for this study.

10.0 APPENDICES WITH SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

[Appendix 1:](#) Regulatory, Ethical, and Study Oversight Considerations

[Appendix 2:](#) Clinical Laboratory Tests

[Appendix 3:](#) AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

[Appendix 4:](#) Contraceptive and Barrier Guidance

[Appendix 5:](#) Measures to Ensure Subject Safety and Management of Medical Emergencies

[Appendix 6:](#) Protocol Amendment History

10.1 Appendix 1: Regulatory, Ethical, and Trial Oversight Considerations

10.1.1 Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- 21CFR Parts 50, 54, 56 and 312;
- Applicable ICH Good Clinical Practice (GCP) Guidelines;
- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS); and
- Applicable local laws and regulations.

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator is responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC at least annually, in accordance with the requirements, policies, and procedures established by the IRB/IEC;
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures; and

Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, and all other applicable local regulations.

10.1.2 Financial Disclosure

Investigators must provide financial disclosure information to allow the Sponsor to submit complete and accurate certification or disclosure statements to the appropriate regulatory authorities. In addition, Investigators must provide to the Sponsor a commitment to promptly update this information if any relevant changes occur during the investigation and for 1 year following the completion of the study.

Neither the Sponsor nor their Contract or Clinical Research Organization (CRO) partner is financially responsible for additional testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, neither the Sponsor nor their CRO are financially responsible for further treatment of the subject's disease.

10.1.3 Informed Consent

An informed consent form (ICF) meeting the requirements of 21 CFR §50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements (where applicable), must be reviewed and approved by the Sponsor, approved by the IRB before use, and available for inspection.

The Investigator or authorized representative will explain the nature of the study to the subject and answer all questions regarding the study. Subjects must be informed that their participation is voluntary, and if they choose to participate, will be required to sign the approved ICF. The medical record must include a statement that written informed consent was obtained before any study procedures were performed, along with the date written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF. The original signed ICF will be retained in the Investigator's records, with a copy provided to the subject.

The ICF must be revised if new information becomes available during the study that may be relevant to the subject. Any revision(s) must be submitted to the appropriate IRB for review and approval in advance of use. Subjects must be re-consented to the most current version of the ICF during their participation in the study.

Subjects who are re-screened are required to sign a new ICF if it has been more than 30 days from the initial consent date.

10.1.4 Data Protection

Subjects will be sequentially assigned a study number at screening that will be used throughout the study. All subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or other identifiable information will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject during the informed consent process ([Section 10.1.3](#)).

Subject medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited. All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain subject confidentiality. All records will be kept in a secure storage area with limited access. Upon the subject's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by health authority inspectors.

All information provided by the Sponsor, verbally and in writing, is confidential. The Investigator agrees not to disclose any such information without prior written permission of the Sponsor. This document may be disclosed to study personnel under the Investigator's supervision and to the IRB under the condition that they also agree to maintain its confidentiality. Any supplemental information (e.g., protocol amendment) that may be added to this document is confidential and must also be handled accordingly. The information obtained from the Sponsor may be disclosed to obtain informed consent from subjects who wish to participate in the study.

Study documents provided by the Sponsor (protocols, IB, etc.) will be stored appropriately to ensure their confidentiality.

The Investigator and all employees and co-workers involved with this study may not disclose or use for any purpose other than performance of the study any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any said confidential information to other parties.

10.1.5 Data Quality Assurance

All subject data relating to the study will be recorded on eCRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

Sponsor designated study monitors will perform ongoing source data verification to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

The Sponsor or designee is responsible for the data management of this study including quality checking of the data.

The Sponsor assumes accountability for actions delegated to other individuals (e.g., CROs).

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 10 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.6 Source Documents

All medical information obtained at each study visit must be recorded in the subject's record (source documentation) in real time as it is collected. Source documentation consists of original subject documents, as well as data and records with information relevant to the subject and his/her participation in the study.

Source documents consist of, but are not limited to, subject hospital charts, clinic notes, subject medical records, original test results, laboratory data, worksheets, drug accountability records, consent forms, telephone records, etc. Source documents must be available for review and inspection during on-site monitoring of the study by the Sponsor, their designees, the IRB, and/or appropriate regulatory authorities.

Subject-completed forms are also considered source data. Only subjects are to record information in subject diaries and questionnaires, if used. In no instance, should an Investigator or study site personnel record any data or make changes to subject-completed forms. The Investigator or designee should review subject-completed forms during study visits. If an entry is found to be illegible or a mistake is found (e.g., incorrect year was recorded), the subject may be instructed to edit the entry.

10.1.7 Study and Site Start and Closure

First Act of Recruitment

The study start date is the date on which the clinical study will be open for recruitment of subjects.

Study Termination

The Sponsor or designee reserves the right to close or terminate the study at any time for any reason at the sole discretion of the Sponsor. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

For study termination:

- Discontinuation of further study intervention development.

For site termination:

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines;
- Inadequate or no recruitment (evaluated after a reasonable amount of time) of subjects by the Investigator; and/or
- Total number of subjects included earlier than expected.

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly contact subjects to arrange final study visit(s) and procedures, as directed by the Sponsor.

10.1.8 Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.1.9 Institutional Review Board

The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an IRB by the Investigator and reviewed and approved by the IRB before the study is initiated.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study subjects. Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The Investigator will provide written summaries of the status of the study and any other significant safety findings to the IRB annually or more frequently in accordance with its requirements, policies, and procedures. At the end of the study, the Investigator will notify the IRB of the conclusion of the study and its outcome.

10.2 Appendix 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• Monocytes
	White blood cell count (WBC)		
	Red blood cell (RBC) count		
	Hemoglobin (Hgb)		
	Hematocrit (Hct)		
	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, 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](#).

10.3 Appendix 3: AEs and SAEs: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1 Definition of AE

AE Definition
<ul style="list-style-type: none"> An AE is any untoward medical occurrence in a clinical study subject, temporally associated with the use of study intervention, whether or not considered related to the study intervention. NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Definition of Unsolicited and Solicited AE
<ul style="list-style-type: none"> An unsolicited AE is an AE that was not solicited using a Subject Diary and that is communicated by a subject or subject's parent(s)/ legally authorized representative (LAR) who has signed the informed consent. Unsolicited AEs include serious and non-serious AEs. Potential unsolicited AEs may be medically attended (i.e., symptoms or illnesses requiring a hospitalization, or emergency room visit, or visit to/by a health care provider). The subjects or subject's parent(s)/LAR will be instructed to contact the site as soon as possible to report medically attended event(s), as well as any events that, though not medically attended, are of subject or parental/LAR's concern. Detailed information about reported unsolicited AEs will be collected by qualified site personnel and documented in the subject's records. Unsolicited AEs that are not medically attended nor perceived as a concern by the subject or subject's parent(s)/LAR(s) will be collected during interview with the subject or subject's parent(s)/LAR(s) and by review of available medical records at the next visit. Solicited AEs are predefined local (at the injection site) and systemic events for which the subject is specifically questioned, and which are noted by the subject in their diary.

Events Meeting the AE Definition
<ul style="list-style-type: none"> Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from Baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. Signs, symptoms, or the clinical sequelae of a suspected intervention- intervention interaction. Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose, per se, will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events <u>NOT</u> Meeting the AE Definition
<ul style="list-style-type: none"> Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition. The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition. Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE. Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2 Definition of SAE

An SAE is defined as any serious AE that, at any dose:
<ul style="list-style-type: none"> Results in death
<ul style="list-style-type: none"> Is life-threatening <p>The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.</p>
<ul style="list-style-type: none"> Requires inpatient hospitalization or prolongation of existing hospitalization <ul style="list-style-type: none"> In general, hospitalization signifies that the subject has been admitted (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from Baseline is not considered an AE.
<ul style="list-style-type: none"> Results in persistent or significant disability/incapacity <ul style="list-style-type: none"> The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
<ul style="list-style-type: none"> Is a congenital anomaly/birth defect
<ul style="list-style-type: none"> Other situations: <ul style="list-style-type: none"> Medical or scientific judgment should be exercised by the Investigator in deciding whether SAE reporting is appropriate in other situations such as significant medical events that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such events include invasive or malignant cancers, intensive treatment for allergic bronchospasm, blood dyscrasias, convulsions or development of intervention dependency or intervention abuse.

10.3.3 Recording and Follow-Up of AE and/or SAE

AE and SAE Recording
<ul style="list-style-type: none"> • When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event. • The Investigator will then record all relevant AE/SAE information. • It is not acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor or designee in lieu of completion of SAE/AE required form. • There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor or designee. • The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
Assessment of Intensity
<p>The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:</p> <ul style="list-style-type: none"> • Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities. • Moderate: An event that causes sufficient discomfort to interfere with normal everyday activities. • Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe. • An event is defined as 'serious' when it meets at least one of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality
<ul style="list-style-type: none"> • The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. • A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. • The Investigator will use clinical judgment to determine the relationship. • Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. • The Investigator will also consult the IB and/or Product Information, for marketed products, in his/her assessment. • For each AE/SAE, the Investigator must document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality. • There may be situations in which an SAE has occurred, and the Investigator has minimal information to include in the initial report to The Sponsor. However, it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to The Sponsor. • The Investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. • The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
<ul style="list-style-type: none"> • The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide The Sponsor with a copy of any postmortem findings including histopathology. • New or updated information will be recorded in the originally submitted documents. • The Investigator will submit any updated SAE data to The Sponsor within 24 hours of receipt of the information.

10.3.4 Reporting of SAEs

SAE Reporting via the Electronic Data Collection (EDC) System
<ul style="list-style-type: none"> • The primary mechanism for reporting an SAE will be the EDC system. • If the EDC system is unavailable, then the site will use the paper SAE data collection tool (see next Section) to report the event within 24 hours. • The site will enter the SAE data into the EDC system as soon as it becomes available. • After the study is completed at a given site, the EDC system will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the EDC system has been taken off-line, then the site can report this information as specified in Section 8.3.4. • Contacts for SAE reporting can be found in Section 8.3.4.

SAE Reporting via Paper Data Collection Tool
<ul style="list-style-type: none"> • It is the responsibility of the Investigator to report SAEs to the Sponsor within 24 hours of awareness of the event or safety information, whether initial or follow-up. Do not delay in the reporting of suspected SAE in order to obtain additional information. Any additional information, if collected, can be reported as a follow-up to the initial report. • In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service. • Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE data collection tool within the designated reporting time frames. • Contacts for SAE reporting can be found in the Section 8.3.4.

10.4 Appendix 4: Contraceptive and Barrier Guidance

10.4.1 Definitions

Women of Childbearing Potential (WOCBP)

WOCBP are defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal (defined below).

A female is considered fertile following menarche and until becoming postmenopausal unless permanently sterile through hysterectomy, bilateral oophorectomy, and/or bilateral salpingectomy.

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women of Non-childbearing Potential (WONCBP)

Females in the following categories are considered WONCBP (documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview):

- Premenarchal; or
- Premenopausal female with one of the following:
 - Documented hysterectomy.
 - Documented bilateral salpingectomy.
 - Documented bilateral oophorectomy.
- Postmenopausal females (see below).

For individuals with permanent infertility due to an alternate medical cause other than the above, (e.g., Müllerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Postmenopausal Female

A postmenopausal female is defined as one who has had no menses for 12 months without an alternative medical or biological cause. Postmenopausal females must have a documented serum follicle-stimulating hormone (FSH) and estradiol levels consistent with menopause as per reference laboratory ranges at screening to confirm menopause. In the absence of 12 months of amenorrhea, confirmation with *at least two (2)* FSH measurements is required. A pregnancy test is required until both FSH measurements have been collected and results have been received that verify the postmenopausal state of the female subject.

Females on hormone replacement therapy (HRT) and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods (defined below) if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

Highly Effective Methods of Female Contraception

Highly effective methods of female contraception have a failure rate of <1% when used consistently and correctly and may include the following:

- Hormonal methods of contraception, including oral contraceptives containing combined estrogen and progesterone, a vaginal ring, injectable and implantable hormonal contraceptives, intrauterine hormone-releasing system (e.g., Mirena) and progestogen-only hormonal contraception associated with inhibition of ovulation;
- Nonhormonal intrauterine device (IUD);
- Bilateral tubal occlusion;
- Vasectomised subject/partner with documented azoospermia 90 days after procedure, if that partner is the sole sexual partner; and/or
- Complete abstinence, defined as the complete avoidance of heterosexual intercourse. This is an acceptable form of contraception if used consistently throughout the duration of study and for the durations after dosing specified for males and females above. It is not necessary to use any other method of contraception when complete abstinence is elected. WOCBP who choose complete abstinence must continue to have pregnancy tests, per the protocol SoA.

Methods of contraception that are *not* considered highly effective include methods that do not result in a failure rate of <1% per year (e.g., cap, diaphragm, or sponge with spermicide, or male or female condom with or without spermicide), periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods), and withdrawal.

10.4.2 Contraception and Barrier Guidance

Investigators will counsel WOCBP and male participants who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators will advise on the use of an adequate methods of contraception, which is defined as use of a condom by the male partner combined with use of a highly effective method of contraception (defined in [Section 10.4.1](#)) by the female partner.

For Women of Childbearing Potential

WOCBP must agree to remain abstinent (complete avoidance of heterosexual intercourse) or use adequate contraceptive methods, defined as use of a condom by the male partner *combined with* use of a highly effective method of contraception (defined in [Section 10.4.1](#)) by the female partner, during the treatment period and for *at least 32 days* (5 half-lives plus 30-days) after the last dose of study intervention.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

For Male Subjects with Female Partners

Male participants must inform their female partners who are WOCBP of the contraceptive requirements of the protocol and are expected to adhere to using contraception with their partner.

Male participants with female sexual partners must agree to remain as abstinent (complete avoidance of heterosexual intercourse) or use adequate contraceptive methods, defined as use of a condom by the male partner *combined with* use of a highly effective method of contraception (defined in [Section 10.4.1](#)) by the female partner, during the treatment period and for *at least 92 days* (5 half-lives + 90-day spermatogenesis cycle) after the last dose of study intervention.

Male participants must not donate sperm for *at least 92 days* (5 half-lives + 90-day spermatogenesis cycle) after the last dose of study intervention.

Male participants with potentially postmenopausal partners who are under the age of 55 years must use condoms unless their partner's postmenopausal status has been confirmed by FSH level.

For Male Subjects with Same-Sex Partners or with WONCBP Partners

Male participants in same-sex relationships or in relationships with WONCBP must agree to remain abstinent (complete avoidance of intercourse) or use a condom to prevent exposure of the partner to study intervention through ejaculate/seminal fluid during the treatment period and for *at least 92 days* (5 half-lives + 90-day spermatogenesis cycle) after the last dose of study intervention.

10.5 Appendix 5: Measures to Ensure Subject Safety and Management of Medical Emergencies

10.5.1 Facilities and Attending Staff

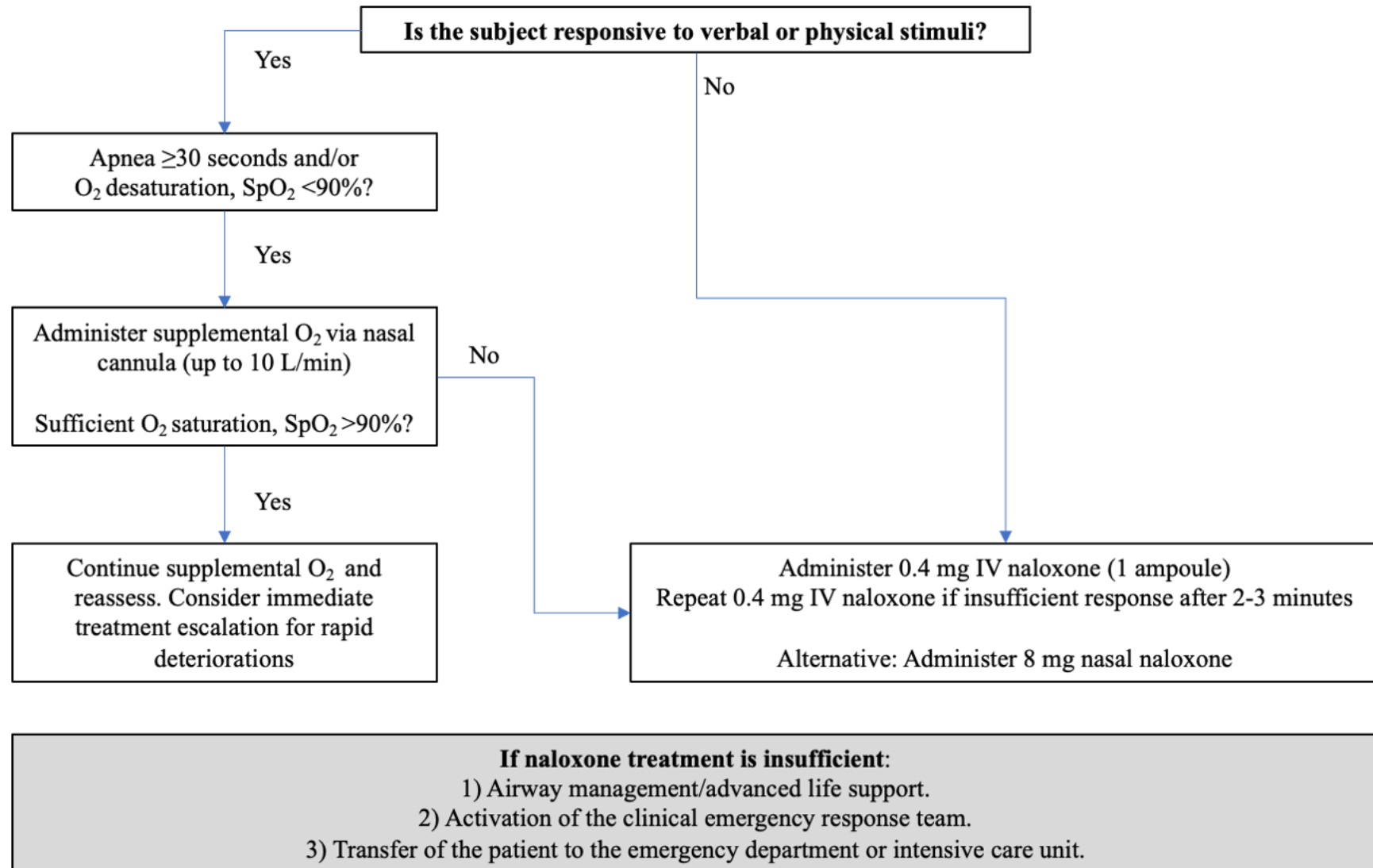
This study will be conducted by a team of licensed physicians, nurse practitioners and nurses at the Frontage Laboratories CRU. All medical staff are BLS and ACLS certified. The study will include continuous monitoring of vital signs and oxygen saturation as well as frequent assessments of respiratory function and ECGs for all study subjects following administration of study drugs. The CRU is close to the local regional hospital with an Emergency Department and several intensive care units. Clinical medical staff will be available on call 24 hours a day throughout the duration of the study and will include a physician/nurse practitioner and nurse trained and equipped for handling acute clinical emergencies.

10.5.2 Management of Medical Emergencies

The emergency flow chart for management of excessive respiratory depression is provided in Figure 3.

Available emergency equipment includes emergency medication (e.g., naloxone, midazolam, H1-antagonists, anesthetics) and airway management equipment (e.g., resuscitation bag, masks, laryngoscope, endotracheal tubes, supraglottic airway devices). The emergency medication and equipment will be reviewed for sufficiency by the attending physician anesthesiologists prior to initiation of this study.

Because opioid-induced respiratory depression is considered the most likely medical emergency, naloxone will be available for rapid intravenous or alternatively intranasal administration. Furthermore, the emergency flow chart below (Figure 3) for respiratory depression will be communicated with all team members and will be available in a printed form at the CRU as a guideline for treating opioid-induced respiratory depression. Other medical emergencies will be handled at the discretion of the attending physician.

Figure 3: Emergency Flow Chart for Management of Excessive Respiratory Depression

10.6 Appendix 6: Normal Ranges for Laboratory Values

10.6.1 Normal Ranges for Laboratory Values

Parameter	Normal Range
WBC	M: 3.66-10.60 x10(3)/uL F: 4.00-10.10 x10(3)/uL
RBC	M: 3.94-5.76 x10(6)/uL F: 3.58-5.19 x10(6)/uL
Hemoglobin	M: 12.0-16.9 g/dL F: 11.0-15.5 g/dL
Hematocrit	M: 34.6-49.6 % F: 31.5-44.8 %
Platelet Count	140-425 x10(3)/uL
Calcium, Total	8.6-10.4 mg/dL
Magnesium	1.6-2.4 mg/dL
Bilirubin, Total	<1.2 mg/dL
Alkaline Phosphatase	40-156 U/L
AST	M: <40 U/L F: <32 U/L
ALT	M: <41U/L F: <33 U/L
Glucose	70-99 mg/dL
BUN	6-20 mg/dL
Creatinine	M: 0.67-1.31 mg/dL F: 0.49-1.02 mg/dL
Sodium	135-147 mmol/L
Potassium	3.5-5.5 mmol/L
Chloride	96-108 mmol/L
CO ₂	19-29 mmol/L
Estimated Glomerular Filtration Rate	≥60 mL/min

10.7 Appendix 7: Protocol Amendment History

The amendment history for Protocol QEV-817-101 is provided in [Table 6](#).

Table 6: Protocol QEV-817-101: Amendment History

Version	Version Date	Brief Description and Rationale
7.1	23 Sept 2025	Clarification of data reporting and analysis endpoints for safety and tolerability and pharmacokinetics in Section 9.5 (Statistical Analyses) and secondary endpoints (Section 3.0 – Objectives and Endpoints)
7.0	04 Aug 2025	----[REDACTED]-----
		----[REDACTED]-----

11.0 REFERENCES

Websites:

1. DOPRAM Injection (doxapram hydrochloride injection, USP) US Label for NDA 014879. Updated in 2005. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/14879s044lbl.pdf. Accessed 11 March 2024.
2. Schiller EY, Goyal A, and Mechanic OJ. 2023. 'Opioid Overdose', StatPearls Publishing. Copyright © 2023, StatPearls Publishing LLC., Available at: <https://www.ncbi.nlm.nih.gov/books/NBK470415/>. Accessed 29 August 2023.

Literature:

3. -----[REDACTED]-----
4. Bairam A, Blanchard PW, Mullahoo K, *et al.* 1990. Pharmacodynamic effects and pharmacokinetic profiles of keto-doxapram and doxapram in newborn lambs. *Pediatr Res*, 28: 142–46.
5. Bairam A, Akramoff-Gershan L, Beharry K, *et al.* 1991. Gastrointestinal absorption of doxapram in neonates. *Am J Perinatol*, 8: 110–13.
6. Bairam A, Faulon M, Monin P, *et al.* 1992. Doxapram for the initial treatment of idiopathic apnea of prematurity. *Biol Neonate*, 61: 209–13.
7. Barbé F, Hansen C, Badonnel Y, *et al.* 1999. Severe side effects and drug plasma concentrations in preterm infants treated with doxapram. *Ther Drug Monit*, 21: 547–52.
8. Barrington KJ, Finer NN, Peters KL, *et al.* 1986. Physiologic effects of doxapram in idiopathic apnea of prematurity. *J Pediatr*, 108: 124–29.
9. Barrington KJ, Finer NN, Torok-Both G, *et al.* 1987. Dose-response relationship of doxapram in the therapy for refractory idiopathic apnea of prematurity. *Pediatrics*, 80: 22–27.
10. Beaudry MA, Bradley JM, Gramlich LM, *et al.* 1988. Pharmacokinetics of doxapram in idiopathic apnea of prematurity. *Dev Pharmacol Ther*, 11: 65–72.
11. Bhardwaj H, Bhardwaj B, and Awab A. 2014. Revisiting opioid overdose induced acute respiratory distress syndrome. *Indian J Crit Care Med*, 18: 119–20.
12. Brown T and Stoudemire A. 1998. Psychiatric side effects of prescription and over-the-counter medications. *Recognition and management* (American Psychiatric Press: Washington, DC).
13. Chang HY, Daubresse M, Kruszewski SP, *et al.* 2014. Prevalence and treatment of pain in EDs in the United States, 2000 to 2010. *Am J Emerg Med*, 32: 421–31.

14. Dahan A, Aarts L, and Smith TW. 2010. Incidence, Reversal, and Prevention of Opioid-induced Respiratory Depression. *Anesthesiology*, 112: 226–38.
15. Dahan A, van der Schrier, Smith T, *et al.* 2018. Averting Opioid-induced Respiratory Depression without Affecting Analgesia. *Anesthesiology*, 128: 1027–37.
16. Darwish M, Bond M, Ma Y, *et al.* 2017. Abuse Potential with Oral Route of Administration of a Hydrocodone Extended-Release Tablet Formulated with Abuse-Deterrence Technology in Nondependent, Recreational Opioid Users. *Pain Med*, 18: 61–77.
17. Daubresse M, Chang HY, Yu Y, *et al.* 2013. Ambulatory diagnosis and treatment of nonmalignant pain in the United States, 2000-2010. *Med Care*, 51: 870–78.
18. "Dopram®-V (doxapram hydrochloride injection) [Prescribing Information]." In. 2010. St. Joseph, MO: Boehringer Ingelheim Vetmedica, Inc.
19. Ducoulombier V, Chiquet R, Graf S, *et al.* 2020. Usefulness of a visual analog scale for measuring anxiety in hospitalized patients experiencing pain: a multicenter cross-sectional study. *Pain Management Nursing*, 21: 572-78.
20. Flint R, Simmons S, Andriessen P, *et al.* 2021. The bioavailability and maturing clearance of doxapram in preterm infants. *Pediatric research*, 89: 1268–77.
21. Golder FJ, Hewitt MM, and McLeod JF. 2013. Respiratory stimulant drugs in the post-operative setting. *Respir Physiol Neurobiol*, 189: 395–402.
22. Gupta P and Dundee J. 1974. Morphine combined with doxapram or naloxone. A study of post-operative pain relief. *Anaesthesia*, 29: 33–39.
23. -----[REDACTED]-----
24. Han B, Compton WM, Blanco C, *et al.* 2017. Prescription Opioid Use, Misuse, and Use Disorders in U.S. Adults: 2015 National Survey on Drug Use and Health. *Ann Intern Med*, 167: 293–301.
25. Harris S, Cipriano A, Colucci S, *et al.* 2017. Oral Abuse Potential, Pharmacokinetics, and Safety of Once-Daily, Single-Entity, Extended-Release Hydrocodone (HYD) in Recreational Opioid Users. *Pain Med*, 18: 1278–91.
26. Hayakawa F, Hakamada S, Kuno K, *et al.* 1986. Doxapram in the treatment of idiopathic apnea of prematurity: desirable dosage and serum concentrations. *J Pediatr*, 109: 138–40.
27. Kim SI, Winnie AP, Collins VJ, *et al.* 1971. Hemodynamic responses to doxapram in normovolemic and hypovolemic dogs. *Anesth Analg*, 50: 705–10.
28. -----[REDACTED]-----
29. Maillard C, Boutroy MJ, Fresson J, *et al.* 2001. QT interval lengthening in premature infants treated with doxapram. *Clin Pharmacol Ther*, 70: 540–45.

30. Martinez JM, Garakani A, Aaronson CJ, *et al.* 2015. Heart rate and respiratory response to doxapram in patients with panic disorder. *Psychiatry Res*, 227: 32–38.
31. Modalen ÅÖ, Quiding H, Frey J, *et al.* 2006. A novel molecule with peripheral opioid properties: the effects on hypercarbic and hypoxic ventilation at steady-state compared with morphine and placebo. *Anesthesia & Analgesia*, 102: 104-09.
32. Murphy SL, Xu J, and Kochanek KD. 2013. Deaths: final data for 2010. *Natl Vital Stat Rep*, 61: 1–117.
33. Nahin RL. 2015. Estimates of pain prevalence and severity in adults: United States, 2012. *J Pain*, 16: 769–80.
34. Nardi AE, Freire RC, and Zin WA. 2009. Panic disorder and control of breathing. *Respir Physiol Neurobiol*, 167: 133–43.
35. Ossiander EM. 2014. Using textual cause-of-death data to study drug poisoning deaths. *Am J Epidemiol*, 179: 884–94.
36. Overdyk FJ, Carter R, Maddox RR, *et al.* 2007. Continuous oximetry/capnometry monitoring reveals frequent desaturation and bradypnea during patient-controlled analgesia. *Anesth Analg*, 105: 412–18.
37. Paulozzi LJ, Weisler RH, and Patkar AA. 2011. A national epidemic of unintentional prescription opioid overdose deaths: how physicians can help control it. *J Clin Psychiatry*, 72: 589–92.
38. Poppe J, van Weteringen W, Sebek L, *et al.* 2020. Precision dosing of doxapram in preterm infants using continuous pharmacodynamic data and model-based pharmacokinetics: An illustrative case series. *Front Pharmacol*, 11: 665.
39. Prins SA, Pans SJ, van Weissenbruch MM, *et al.* 2013. Doxapram use for apnoea of prematurity in neonatal intensive care. *Int J Pediatr*, 2013: 251047.
40. Randall N, Pleuvry B, Fazackerley E, *et al.* 1989. Effect of oral doxapram on morphine-induced changes in the ventilatory response to carbon dioxide. *Br J Anaesth*, 62: 159–63.
41. Robson R and Prescott L. 1978. A pharmacokinetic study of doxapram in patients and volunteers. *Br J Clin Pharmacol*, 7: 81–87.
42. Romberg R, Olofsen E, Sarton E, *et al.* 2003. Pharmacodynamic effect of morphine-6-glucuronide versus morphine on hypoxic and hypercapnic breathing in healthy volunteers. *The Journal of the American Society of Anesthesiologists*, 99: 788-98.
43. Romeo M, Betta P, Tina L, *et al.* 1995. Oral administration of doxapram in preterm neonates with aminophylline-resistant idiopathic apnea crisis [original in Italian]. *Pediatr Med Chir*, 17: 123–26.

44. Roozkrans M, Olofsen E, van der Schrier R, *et al.* 2017. Doxapram-mediated Increase in Cardiac Output Reduces Opioid Plasma Concentrations: A Pharmacokinetic/Pharmacodynamic–Pharmacokinetic/Pharmacodynamic Modeling Study in Healthy Volunteers. *Clinical Pharmacology & Therapeutics*, 102: 115-22.
45. Rudd R, Aleshire N, Zibbell J, *et al.* 2016. Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014. *MMWR Morb Mortal Wkly Rep*, 65: 1445–52.
46. Sardinha A, Freire RC, Zin WA, *et al.* 2009. Respiratory manifestations of panic disorder: causes, consequences and therapeutic implications. *J Bras Pneumol*, 35: 698–708.
47. Shapiro A, Zohar E, Zaslansky R, *et al.* 2005. The frequency and timing of respiratory depression in 1524 postoperative patients treated with systemic or neuraxial morphine. *J Clin Anesth*, 17: 537–42.
48. Stephen CR and Talton I. 1966. Effects of doxapram on the electrocardiogram during anesthesia. *Anesth Analg*, 45: 783–89.
49. -----[REDACTED]-----
50. Ten Hove CH, Vliegthart RJ, Te Pas AB, *et al.* 2016. Long-Term Neurodevelopmental Outcome after Doxapram for Apnea of Prematurity. *Neonatology*, 110: 21–26.
51. Teppema LJ and Dahan A. 2010. The ventilatory response to hypoxia in mammals: mechanisms, measurement, and analysis. *Physiol Rev*, 90: 675–754.
52. Vallner J, Stewart J, Kotzan J, *et al.* 1981. Pharmacokinetics and bioavailability of hydromorphone following intravenous and oral administration to human subjects. *The Journal of Clinical Pharmacology*, 21: 152-56.
53. Webster LR, Hansen E, Stoddard GJ, *et al.* 2022. Ventilatory response to hypercapnia as experimental model to study effects of oxycodone on respiratory depression. *Current Reviews in Clinical and Experimental Pharmacology Formerly Current Clinical Pharmacology*, 17: 72-80.
54. White JM and Irvine RJ. 1999. Mechanisms of fatal opioid overdose. *Addiction*, 94: 961–72.
55. Williams VS, Morlock RJ, and Feltner D. 2010. Psychometric evaluation of a visual analog scale for the assessment of anxiety. *Health and quality of life outcomes*, 8: 1-8.
56. Yost CS. 2006. A new look at the respiratory stimulant doxapram. *CNS drug reviews*, 12: 236-49.