BIOEQUIVALENCE STUDY PROTOCOL

COMPARATIVE RANDOMIZED, SINGLE DOSE, TWO-WAY CROSSOVER OPEN LABEL STUDY TO DETERMINE THE BIOEQUIVALENCE OF *5 MG/ML TRAMADOL HYDROCHLORIDE ORAL SOLUTION (08P1902F0)* RELATIVE TO *CONTRAMAL® (100 MG/ML ORAL SOLUTION)* AFTER AN ORAL ADMINISTRATION TO HEALTHY ADULTS UNDER FASTING CONDITIONS

Study code: UP-CLI-2021-001
Version 1.0 – 13 February 2022

Sponsor	**UNITHER Pharmaceuticals** 3-5 Rue Saint-Georges 75009 Paris France
Test product	*5 mg/mL Tramadol Hydrochloride Oral Solution (08P1902F0)*
Development Phase	Bioequivalence Study
EudraCT number	2021-004916-24
CRO:	**International Pharmaceutical Research Center (IPRC)** [redacted]

AMENDMENT POLICY

Protocol Amendments are to be written if any procedure in the Protocol needs to be changed. It must be signed by the principal investigator and the Sponsor. Only if all signatures are available, the Protocol Amendment can be considered approved.

Signatures may-where necessary-be submitted by Fax or e-mail. All amendments are to be sent to and approved by the IRB.

The study must not begin or continue before the IRB gives its written approval.

COMPARATIVE RANDOMIZED, SINGLE DOSE, TWO-WAY CROSSOVER OPEN LABEL STUDY TO DETERMINE THE BIOEQUIVALENCE OF *5 MG/ML TRAMADOL HYDROCHLORIDE ORAL SOLUTION (08P1902F0)* RELATIVE TO *CONTRAMAL® (100 MG/ML ORAL SOLUTION)* AFTER AN ORAL ADMINISTRATION TO HEALTHY ADULTS UNDER FASTING CONDITIONS

Sponsor:	**UNITHER Pharmaceuticals**
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Address:	Sport City Circle, Amman, Jordan. [redacted]
Clinical Site:	IPRC Clinical Site
Analytical Site:	IPRC Analytical laboratories.

[redacted]

IPRC's Protocol Revisions and Approvals

Comparative Randomized, Single Dose, Two-Way Crossover Open Label Study To Determine The Bioequivalence Of *5 mg/mL Tramadol Hydrochloride Oral Solution (08P1902F0)* Relative To *Contramal®* *(100 mg/mL Oral Solution)* After An Oral Administration To Healthy Adults Under Fasting Conditions

[redacted]

SPONSOR'S REPRESENTATIVE PROTOCOL REVISIONS AND APPROVALS

COMPARATIVE RANDOMIZED, SINGLE DOSE, TWO-WAY CROSSOVER OPEN LABEL STUDY TO DETERMINE THE BIOEQUIVALENCE OF *5 MG/ML TRAMADOL HYDROCHLORIDE ORAL SOLUTION (08P1902F0)* RELATIVE TO *CONTRAMAL®* *(100 MG/ML ORAL SOLUTION)* AFTER AN ORAL ADMINISTRATION TO HEALTHY ADULTS UNDER FASTING CONDITIONS

PRINCIPAL INVESTIGATOR RESPONSIBILITIES

COMPARATIVE RANDOMIZED, SINGLE DOSE, TWO-WAY CROSSOVER OPEN LABEL STUDY TO DETERMINE THE BIOEQUIVALENCE OF *5 MG/ML TRAMADOL HYDROCHLORIDE ORAL SOLUTION (08P1902F0)* RELATIVE TO *CONTRAMAL®* *(100 MG/ML ORAL SOLUTION)* AFTER AN ORAL ADMINISTRATION TO HEALTHY ADULTS UNDER FASTING CONDITIONS

I, the undersigned, agree:

[redacted]

TABLE OF CONTENTS

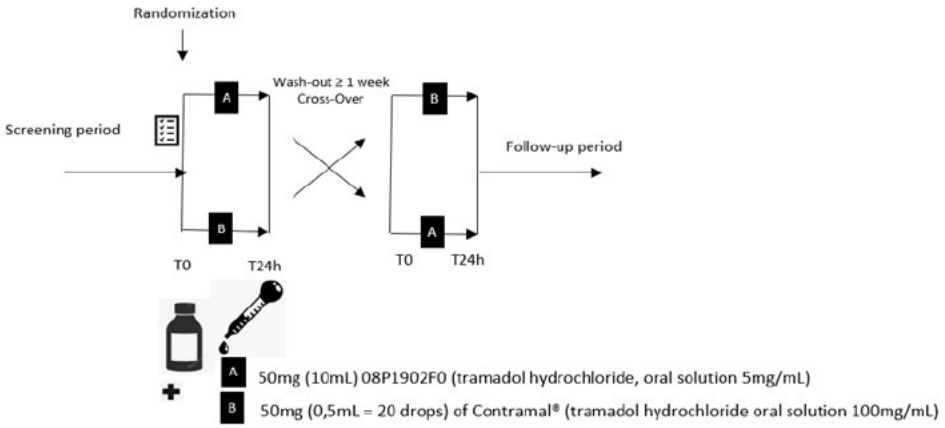
List of Abbreviations

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
ALP	Alkaline Phosphatase
ANOVA	Analysis Of Variance
ATC	Anatomic Therapeutic Chemical classification
AUC	Area Under the plasma concentration-time Curve
$AUC_{0\rightarrow t}$	Area Under the plasma concentration-time Curve from zero (0) hours to time (t) hours
$AUC_{0\rightarrow\infty}$	Area Under the plasma concentration-time Curve from zero (0) hours to infinity (∞)
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
°C	Celsius
cm	Centimeter
C_{max}	Maximal Plasma Concentration.
CNS	Central Nervous System
COVID-19	Corona virus Disease 2019
CRF	Case Report Form.
CRO	Contract Research Organization
CYP	Cytochrome P.
CV	Curriculum Vitae
DMU	Data Management Unit
ECG	Electrocardiogram
EMA	European Medicines Agency
g	Gram
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good manufacturing practice
Hr/h	Hour
HBsAg	Hepatitis B surface Antigen
HCG	Human chorionic gonadotropin
HCl	Hydrochloride
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form.
ICH	International Council for Harmonization
IEC	Independent Ethic Committee
IMP	Investigational Medicinal Product
IPRC	International Pharmaceutical Research Center
IRB	Institutional Review Board
ISR	Incurred Sample Reanalysis

List of Abbreviations (Continued)

JFDA	Jordan Food and Drug Administration
K_{el}	Elimination rate constant.
Kg	Kilogram
L	Liter
Log	Logarithm
LogP	log partition coefficient
LLOQ	Lower Limit of Quantification
m^2	meter square
MAOIs	Monoamine Oxidase Inhibitors
MCV	Mean corpuscular volume
MCH	Mean Corpuscular Haemoglobin
MCHC	Mean Corpuscular Haemoglobin -Concentration
mg	milligram
min	minutes
mL	milliliter
mmHg	millimeter of mercury
PCV	Packed cell volume
pH	Measure of the acidity or basicity of a solution.
PKa	Negative log of the acid dissociation constant or Ka value
QTc	is a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle.
QU	Quality Unit
SAE	Serious Adverse Events
SGOT (AST)	Serum Glutamic Oxalate Transaminase (Aspartate Aminotransferase)
SGPT (ALT)	Serum Glutamic Pyruvate Transaminase (Alanine Transaminase)
SmPC	Summary of Product Characteristics
SNRIs	Serotonin and Norepinephrine Reuptake Inhibitors
SOP	Standard Operating Procedure
SSRIs	Selective Serotonin Reuptake Inhibitors
$t_{1/2el}$	Half Life
t_{max}	Time point of maximal plasma concentration

SUMMARY OF MAJOR STUDY DATA

TITLE	Comparative Randomized, Single Dose, Two-Way Crossover Open Label Study To Determine The Bioequivalence Of *5 mg/mL Tramadol Hydrochloride Oral Solution (08P1902F0)* Relative To *Contramal® (100 mg/mL Oral Solution)* After An Oral Administration To Healthy Adults Under Fasting Conditions
OBJECTIVES	**Primary Objective:** The aim of this study is to determine the bioequivalence between Test Product relative and Reference Product in terms of AUC (Area under the curve) and C_{max} after a single oral dose administration of 50 mg tramadol hydrochloride to healthy adults under fasting conditions **Secondary Objective:** To investigate the safety and tolerability of the formulations. [redacted]
STUDY ETHICAL CONDUCTION	The study will be conducted according to the "Declaration of Helsinki". [redacted]
STUDY DESIGN	 [redacted]
STUDY SUBJECTS	Healthy male or female subjects, 18-50 years of age, selected from the Jordan population and fulfilling the selection criteria. 24 male or female subjects plus 1-2 alternates will be admitted to the study. [redacted]
DOSAGE REGIMEN	A single oral dose of 50 mg tramadol hydrochloride oral solution from each product will be administered according to a randomization scheme. [redacted]
ADMISSION AND CONFINEMENT	Subjects will be admitted the night before the study drug administration, supervised for at least 10 hours of overnight fasting, and confined until collecting the 24-hour sample.
ANCILLARY ASSESSMENT	Safety/adverse events, laboratory evaluation, ECG, physical examination, vital signs and evaluation of palatability.

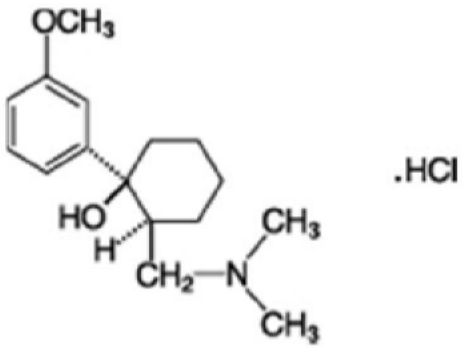
SUMMARY OF MAJOR STUDY DATA (CONTINUED)

BLOOD SAMPLING	Eighteen blood samples will be collected in lithium heparinized tubes before dosing [redacted]
BIOANALYSIS	Drug assays will be carried out using validated chromatographic methods developed specifically for the determination of tramadol in plasma using an achiral assay and its active metabolite O–desmethyltramadol in plasma
PHARMACOKINETICS AND STATISTICAL ANALYSIS	***Primary Pharmacokinetic Parameters of tramadol***: C_{max} and $AUC_{0\rightarrow t}$. [redacted]
BIOEQUIVALENCE CRITERIA	The confidence intervals of logarithmically transformed Test/Reference ratios for C_{max} and $AUC_{0\rightarrow t}$ are set to be within 80.00-125.00%. [redacted]
FINAL REPORT	A comprehensive report will be issued after completion the study.

1. INTRODUCTION

1.1. Chemistry[1]

Tramadol hydrochloride is an opioid agonist. The chemical name for tramadol hydrochloride is (±)cis-2- [(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol hydrochloride. The structural formula is:



The molecular formula of tramadol hydrochloride is $C_{16}H_{25}NO_2 \bullet HCl$, and the molecular weight is 299.8. Tramadol hydrochloride is a white, bitter, crystalline and odorless powder. It is readily soluble in water and ethanol and has a pKa of 9.41. The n-octanol/ water log partition coefficient (logP) is 1.35 at pH 7. Tramadol hydrochloride oral solution (08P1902F0) is a clear, raspberry cherry flavored liquid containing 5 mg of tramadol hydrochloride per 1 mL (equivalent to tramadol 4.4 mg per 1 mL)

1.2. Pharmacological properties[2]

Pharmacotherapeutic group: other opioids; ATC-code: N 02 AX02. Class

Tramadol is a centrally-acting opioid analgesic. It is a non-selective pure agonist at μ, δ and κ opioid receptors with a higher affinity for the μ receptor. Other mechanisms which contribute to its analgesic effect are inhibition of neuronal re-uptake of noradrenaline and enhancement of serotonin release.

Tramadol has also an antitussive effect. In contrast to morphine, analgesic doses of tramadol over a wide range have no respiratory-depressant effect. Also gastrointestinal motility is less affected. Effects on the cardiovascular system tend to be slight.

The potency of tramadol is reported to be 1/10 (one tenth) to 1/6 (one sixth) that of morphine.

1.3. Pharmacokinetic properties[2]

In adults

After a single oral administration of a dose of 50 to 100 mg, the bioavailability is between 70 and 90%.

After oral administration, repeated every 6 hours, of 50 to 100 mg, the state of equilibrium is quickly reached in about 36 hours and the bioavailability increases, exceeding 90%.

The peak serum after oral administration of 100 mg of tramadol is approximately 300 ng / mL (C_{max}) and is reached after approximately 2 h (t_{max}).

Plasma protein binding is 20%, and the volume of distribution is large (3 to 4 l/kg). Tramadol crosses the placental barrier and passes in very small amounts into breast milk (approximately 0.1% of the maternal dose administered).

Elimination half-life is between 5 and 7 hours in healthy volunteers; 90% of tramadol is metabolized, mainly in the liver; one of the demethylated metabolites has an analgesic effect; its half-life is of the same order as that of tramadol.

Tramadol and its metabolites are almost completely excreted via the kidneys (95%). The rest is eliminated in the faeces.

The pharmacokinetics of tramadol are only slightly affected by the age of the patient.

In patients with renal impairment, the clearance of tramadol is reduced in parallel with the clearance of creatinine; the half-life is on average 12 hours.

In hepatic impairment, the clearance of tramadol is reduced, depending on the severity of the hepatic impairment.

1.4. Therapeutic indications[2]

Treatment of moderate to severe pain.

1.5. Special warnings and precautions for use as indicated in SmPC of Contramal®. Some of them are not applicable to the protocol (single dose, adult healthy population, exclusion criteria ect…) [2]

Special warnings

Children and rapid metabolizer

- Those close to the child should be informed that this oral solution should be kept out of reach of children (locked up) to avoid any risk of accidental overdose which could have potentially fatal consequences.
- Cases of ultra-rapid metabolizers have been reported, especially in children.
- Parents should be informed, especially during the first administration, of the need to monitor their child, and to call a doctor or emergency service in case of any unusual signs, including disturbances of consciousness, miosis, vomiting, convulsions or respiratory depression.

Other warnings

Tramadol should be used with particular caution in opioid-dependent patients, in patients predisposed to seizures or in patients with head injury, shock, a reduced level of consciousness of uncertain origin, disorders of the respiratory center or function, increased intracranial pressure.

In opioid dependent patients and in patients with a history of abuse or dependence, treatment should be short-term and under strict medical supervision.

Tramadol is not suitable for substitution therapy in patients with opioid dependence. Although an opioid agonist, tramadol cannot correct the symptoms of opioid withdrawal.

Tolerance and physical and / or psychological dependence can develop even at therapeutic doses. The clinical need for analgesic treatment should be reviewed regularly.

Cases of dependence and abuse have been reported.

Withdrawal symptoms, similar to those which occur with opioid withdrawal, could occur. Withdrawal symptoms can be avoided by gradually reducing the dose when stopping treatment, especially after long periods of treatment.

Special care should be taken when treating patients with respiratory depression or if concomitant CNS depressant drugs are being administered, or if the recommended dosage is significantly exceeded, as the possibility of respiratory depression cannot be excluded in these situations.

Concomitant use of Tramadol with morphine agonist-antagonists (buprenorphine, nalbuphine, pentazocine), and carbamazepine is not recommended.

Alcohol intake during treatment is not recommended.

Convulsions have been reported in patients receiving tramadol at the recommended dose levels. The risk may be increased when doses of tramadol hydrochloride exceed the recommended upper daily dose limit (400 mg). In addition, tramadol may increase the seizure risk in patients taking other medicinal products that lowers the seizure threshold. Patients with epilepsy or those susceptible to seizures should only be treated with tramadol if there are compelling circumstances.

This medicine contains castor oil and may cause digestive problems (mild laxative effect, diarrhea).

This medicine contains a derivative of sucrose. Its use is not recommended in patients with fructose intolerance, glucose-galactose malabsorption syndrome or sucrase-isomaltase deficiency.

Precautions for use

Tramadol should only be used after careful assessment of the risk-benefit ratio, depending on the origin of the pain and the profile of the patient.

1.6. Contraindications[2]

Tramadol is contraindicated

- In hypersensitivity to the active substance or any of the excipients;

- In acute intoxication with alcohol, hypnotics, analgesics, opioids or other psychotropic medicinal products;

- In patients who are receiving MAO inhibitors, especially with linezolid, and methylene blue or who have taken them within the last 14 days;

- In case of severe respiratory failure;

- In children under 3 years old;

- in patients with epilepsy not adequately controlled by treatment;

- for use in narcotic withdrawal treatment.

This medicine should generally not be used:

- during pregnancy.

1.7. Adverse Events[2]

The most commonly reported adverse reactions are nausea and dizziness, both occurring in more than 10 % of patients.

The frequencies are defined as follows:

Very common: ≥1/10

Common: ≥1/100, <1/10

Uncommon: ≥1/1000, <1/100

Rare: ≥1/10 000, <1/1000

Very rare: <1/10 000

Not known: cannot be estimated from the available data

Immune system disorders:

• *Rare:* allergic reaction (eg, dyspnea, bronchospasm, wheezing, angioedema) and anaphylaxis.

Psychiatric disorders:

• *Rare:* hallucinations, confusion, sleep disturbance, delirium, anxiety, nightmares. After administration of tramadol, various psychological side effects may also be observed, the intensity and nature of which vary from one patient to another (depending on the individual reactivity and the duration of the treatment.). changes in mood (usually elation, occasionally dysphoria), changes in activity (usually decreased activity, occasionally increased), and changes in cognitive and sensory abilities (for example, decision behaviour, perception disorders).

Cases of abuse and dependence have been reported as well as cases of withdrawal syndrome.

Withdrawal symptoms, similar to those seen during opioid withdrawal, may occur such as restlessness, anxiety, nervousness, insomnia, hyperkinesia, tremors, and gastrointestinal symptoms.

Other withdrawal symptoms have been reported very rarely, including: panic attack, severe anxiety, hallucinations, paraesthesia, tinnitus, other CNS disorders (eg confusion, delirium, depersonalization, derealization, paranoia).

Nervous system disorders:

- *Very common:* Dizziness
- *Common:* Headache, somnolence
- *Rare:* paraesthesia, tremor, convulsions, involuntary muscle contractions, abnormal coordination, syncope, Speech disorders

Convulsion have mainly occurred after administration of high doses of tramadol or after concomitant treatment with drugs which may lower the seizure threshold.

- *Unknown:* loss of consciousness.

Metabolism and nutrition disorders

- *Rare:* change in appetite.
- *Unknown:* hypoglycemia

Eye disorders:

- *Rare*: miosis, blurred vision, mydriasis.

Cardiovascular disorders:

- *Uncommon:* effects on cardiovascular regulation (palpitation, tachycardia). These side effects may occur especially after intravenous administration and in patients under physical stress.
- *Rare:* bradycardia

Vascular disorders:

- *Uncommon:* effects on cardiovascular regulation (orthostatic arterial hypotension or cardiovascular collapse). These side effects may occur especially after intravenous administration and in patients under physical stress.

Respiratory, thoracic and mediastinal disorders:

- *Rare:* respiratory depression, dyspnea.

Respiratory depression may occur if the doses administered greatly exceed the recommended doses and if other central depressant drugs are administered concomitantly.

Worsening asthma has also been reported, although a causal relationship has not been established.

Gastrointestinal disorders:

• *Very common:* nausea.

• *Common:* Constipation, dry mouth, vomiting.

• *Uncommon:* retching, gastrointestinal irritation (a feeling of pressure in the stomach, bloating), diarrhoea.

Hepatobiliary disorders

• In a few isolated cases an increase in liver enzymes has been reported with the therapeutic use of tramadol.

Skin and subcutaneous tissue disorders

• *Common:* sweating

• *Uncommon:* Dermal reactions (Pruritus, rash, urticaria)

Musculo-skeletal disorders:

• *Rare*: Motorial weakness

Renal and urinary disorders

• *Rare*: Micturition disorders (dysuria and urinary retention)

General disorders and administration site conditions

• *Common:* asthenia

Investigations

• *Rare:* increase in blood pressure

1.8. Interaction with other medicinal products and other forms of interaction[2]

The results of pharmacokinetic studies have so far shown that on the concomitant or previous administration of cimetidine (enzyme inhibitor) clinically relevant interactions are unlikely to occur.

Drugs causing serotonin syndrome

Tramadol can induce convulsions and increase the potential for selective serotonin re-uptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants, anti-psychotics and other seizure threshold-lowering medicinal products (such as bupropion, mirtazapine, tetrahydrocannabinol) to cause convulsions.

Concomitant therapeutic use of tramadol and serotonergic drugs, such as selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), MAO inhibitors, tricyclic antidepressants and mirtazapine may cause serotonin toxicity: diarrhea, tachycardia, sweating, tremors, confusion or even coma

Withdrawal of the serotoninergic medicinal products usually brings about a rapid improvement. Treatment depends on the type and severity of the symptoms.

Other active substances known to inhibit CYP3A4, such as ketoconazole and erythromycin, might inhibit the metabolism of tramadol (N-demethylation) probably also the metabolism of the active O-demethylated metabolite. The clinical importance of such an interaction has not been studied.

Drugs lowering the seizure threshold

The concomitant use of proconvulsant drugs, or drugs lowering the epileptogenic threshold, should be carefully weighed, due to the severity of the risk involved. These drugs are represented in particular by most antidepressants (imipramines, selective serotonin reuptake inhibitors), neuroleptics (phenothiazines and butyrophenones), mefloquine, chloroquine, bupropion, fluoroquinolones, tramadol.

Sedative drugs

It should be taken into account that many drugs or substances can add up their depressant effects on the central nervous system and contribute to reducing vigilance. These are morphine derivatives (analgesics, cough suppressants and substitution treatments), neuroleptics, barbiturates, benzodiazepines, anxiolytics other than benzodiazepines (for example, meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepine, mianserin, mirtazapine, trimipramine), sedating H1 antihistamines, central antihypertensive drugs, baclofen and thalidomide.

Contraindicated combinations

+ Irreversible MAOIs (iproniazid)

Risk of the appearance of a serotonin syndrome: diarrhea, tachycardia, sweating, tremors, confusion or even coma.

Allow two weeks between stopping MAOI and starting treatment with tramadol, and at least one week between stopping tramadol and starting MAOI.

Not recommended associations

+ Morphinic agonists-antagonists (buprenorphine, nalbuphine, pentazocine)

Decrease in the analgesic effect by competitive blocking of receptors, with the risk of the appearance of a withdrawal syndrome.

+ Alcohol (drink or excipient)

Alcohol enhancement of the sedative effect of morphine analgesics.

Impaired alertness can make driving and using machines dangerous.

Avoid taking alcoholic drinks and drugs containing alcohol.

+ Carbamazepine

Risk of decreased plasma concentrations of tramadol.

Co-administration or prior administration of carbamazepine (enzyme inducer) may reduce analgesic effects and shorten the duration of action of tramadol.

+ Reversible MAOIs including linezolid and methylene blue

Risk of the appearance of a serotonin syndrome: diarrhea, tachycardia, sweating, tremors, confusion or even coma.

If the combination cannot be avoided, very close clinical monitoring. Start the combination at the minimum recommended doses.

+ Partial antagonist morphines

Risk of reduction of the analgesic effect.

+ Naltrexone

Risk of reduction of the analgesic effect.

+ Sodium oxybate

Increase in central depression

Impaired alertness can make driving and using machines dangerous.

Combinations subject to precautions for use

+ Antivitamin K

Risk of increased effect of antivitamin K and risk of bleeding. More frequent monitoring of the INR. Possible adjustment of the dose of the antivitamin K during treatment with tramadol and after its discontinuation.

Associations to take into account

+ Other opioid agonist analgesics, morphine-like cough suppressants (dextromethorphan, noscapine, pholcodine), true morphine cough suppressants (codeine, ethylmorphine)

Increased risk of respiratory depression which may be fatal in case of overdose.

+ Other drugs lowering the seizure threshold

Increased risk of convulsion.

+ Other sedative drugs

Increase in central depression.

Impaired alertness can make driving and using machines dangerous.

+ Benzodiazepines and related drugs

Increased risk of respiratory depression which may be fatal in case of overdose.

+ Barbiturates

Increased risk of respiratory depression which may be fatal in case of overdose.

+ MAOI B

Risk of onset of serotonin syndrome.

+ Selective serotonin reuptake inhibitors (citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline)

Risk of onset of seizures and / or serotonin syndrome.

+ Venlafaxine

Risk of onset of seizures and / or serotonin syndrome.

+ Buproprion

Increase in plasma concentrations of tramadol due to decrease in its hepatic metabolism by bupropion. In addition, risk of seizures due to the addition of the effects of the two drugs.

+ Ondansetron

Decreased strength and duration of analgesic effect of tramadol and risk of reduced antiemetic effect of ondansetron.

1.9. Study Medications

Identification	TEST Product -Treatment A	REFERENCE Product-Treatment B
[redacted]	[redacted]	[redacted] /-2 mL of water

2. OBJECTIVES

Primary Objective: This aim of this study is to demonstrate the bioequivalence between Test Product and Reference Product after a single oral dose administration of 50 mg tramadol hydrochloride to healthy adults under fasting conditions. The bioequivalence of a single dose of 50 mg tramadol hydrochloride will be assessed by comparing the pharmacokinetic parameters derived from the plasma concentration-time profiles of tramadol.

Secondary Objective: To investigate the safety and tolerability of the formulations.

[redacted]

2.1. Justification of the study

[redacted]

2.2. Risk to benefit ratio

[redacted]

[redacted]

3. ETHICS CONSIDERATIONS

3.1. Basic Principle

This research will be carried out in accordance with conditions stipulated by International clinical research guidelines and the principles enunciated in the Declaration of Helsinki[3] and the ICH harmonized tripartite guideline regarding Good Clinical Practice (GCP) adopted by the European Medicines Agency[4] guidelines for bioequivalence. In addition, all local regulatory requirements will be adhered to, in particular those which afford greater protection to the safety of the study participants[5].

3.2. Institutional Review Board (IRB)

The Institutional Review Board of the IPRC will review the protocol and the study will not start until the Board has approved the protocol or a modification thereof. The Board is constituted and operates in accordance with the principles and requirements described in the Guidelines on Research Involving Human Subjects[6]. All amendments to the study protocol are to be sent to the IRB for approval.

3.3. Informed Consent

The purpose of the study, the procedures to be carried out and the potential hazards will be described to the subjects in non-technical terms. Subjects will be required to read, sign and date a consent form summarizing the discussion prior to enrolment and will be assured that they may withdraw from the study at any time without jeopardizing their medical care. IPRC will keep the ICF for the subjects also a copy will be given to the subject.

3.4. Subject Confidentiality

All communications and documents relevant to subjects in the study will identify each subject only by the subjects' initials or by the subjects' study numbers.

3.5. Study Completion, Termination or Suspension

The Principal Investigator will complete this study in satisfactory compliance with the study protocol. It is agreed that, for a reasonable cause, either the Principal Investigator, JFDA, IRB or Sponsor may terminate this study prematurely, provided that written notice is submitted at a reasonable time in advance of the intended termination.

[redacted]

insurance company. Each subject will be informed about his indemnity in the Informed Consent

[redacted]

[redacted]

[redacted]

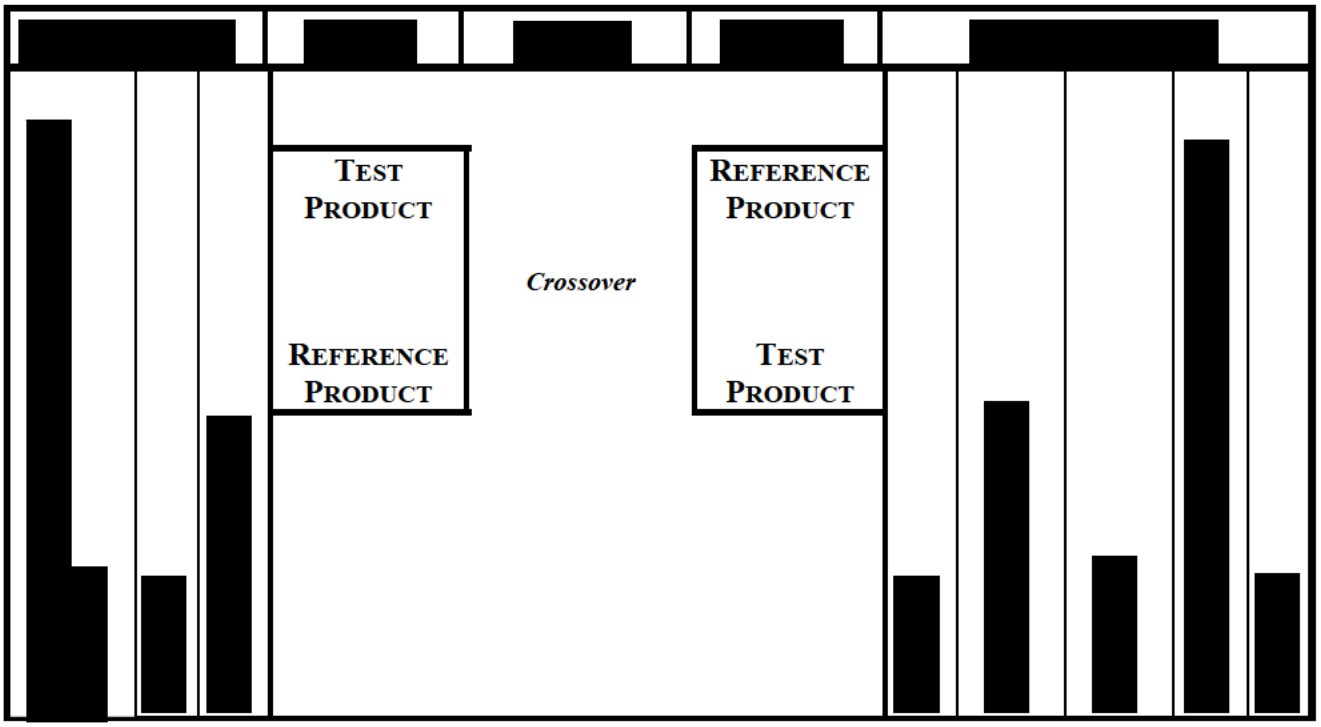
[redacted]

4. INVESTIGATION

4.1. Study Design[7,8]

Open-label, randomized, two-way crossover study to compare the relative bioavailability of tramadol from Test product and Reference Product given as a single dose of 50 mg tramadol hydrochloride under fasting conditions. The subjects who conform to the study entry criteria will be dosed according to a randomization schedule. The plan of study is depicted in Figure 1.

Figure 1 Study Plan



4.2. Facilities

The clinical part of the study will be performed at the IPRC clinical site, a clinical site with examination rooms; procedural laboratories and emergency care equipment. Drug assays will be performed at the IPRC analytical laboratories. Pharmacokinetics and biostatistical analysis will be performed by the data management unit. All facilities are located in Amman, Jordan.

4.3. Laboratory Investigations

Before enrolment in the study, the subjects will undergo clinical laboratory tests performed by the IPRC clinical laboratories.

4.4. Screening and follow up

In case of withdrawals, if the subject received the study's medication at least once, follow-up examinations will be done according to the nature of the withdrawal. If the subject withdraws because of adverse event(s), the Principal Investigator will arrange close monitoring of the subject with the necessary measurements. Subject who have an acute infection within one week preceding study drug administration will not be admitted to the study.

Table 1 Laboratory tests to be performed on subjects.

Tests	Screening	Before admission to period I	Before admission to period II	Follow Up
Haematology				
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]				
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]				
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]	[redacted]			[redacted]
[redacted]				
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]	[redacted]			
[redacted]	[redacted]	[redacted]	[redacted]	

4.5. Study Subjects

24 male or female subjects plus 1-2 alternates will be admitted in the study. [redacted]

4.6. Subject Selection Criteria

To be eligible for participation in the study, subjects must meet all of the following criteria before their enrolment in the study.

4.6.1. Inclusion criteria

1. Healthy subjects male or female, age 18 to 50 years, inclusive.
2. Body weight $\geq$ 50 kg.
3. Body Mass Index (BMI) range[8] is within 18.5 – 30 Kg/m^2.
4. [redacted]

4.6.2. Exclusion criteria

1. Medical history performed not longer than two weeks before the initiation of the clinical study with significant deviations from the normal ranges.

2. Presence of any clinically significant results from laboratory tests, however, ALP and creatinine will be accepted if below the reference range after being evaluated by the physician as clinically not significant. Haematology tests with deviation of more than 5% of the reference limits. Laboratory tests are performed not longer than two weeks before the initiation of the clinical study.

[redacted] prior to first study drug administration until donating the last sample of the study.

[redacted]

5. METHODS AND PROCEDURES

5.1. Drug Supplies and Retention

The Sponsor will supply sufficient quantities of the study Investigational Medicinal Products to allow completion of this study. [redacted]

5.2. Subjects Identification

[redacted]

5.3. Randomization

[redacted]

5.4. Method of administration

Only subjects enrolled in the study may receive investigational product, in accordance with all applicable regulatory requirements. Only authorized site staff may supply or administer investigational product.

[redacted]

[redacted]

[redacted]

[redacted]

5.5. Product return or destruction

At the end of the study, there will be a final reconciliation of product shipped, product consumed, product remaining and treatment disposed. This reconciliation will be recorded in the accountability record form, signed and dated.

Remaining IMP will either be disposed at the study site according to the study site's institutional standard operating procedure or be returned to Creapharm with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Any discrepancies noted will be investigated, resolved and documented prior to destruction.

5.6. Restrictions and Prohibitions

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.7. Study Conduction and Standardization

Subjects will only be included in the study, if they participate in a meeting with the Principal Investigator or the clinical staff about the details of the study, if they give their written informed consent, if they meet the inclusion criteria and do not meet the exclusion criteria, and if the Principal Investigator gives the final approval for the subjects to participate after completion of the screening part. The study is to be conducted as proposed below:

- In the evening before administration on study day 1 of study periods I and II, subjects will be admitted to the clinical site.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- At least 7-day will be allowed between the two doses, as a washout period.

[redacted]

5.8. Sampling Schedule

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.9. End of study

The end-of-study is defined as the date of the last subject's last assessment.

5.10. Subjects Monitoring

[redacted]

5.11. Biological Samples Handling and Storage

Blood samples will be collected at the times specified under the sampling schedule, and centrifuged (using refrigerated centrifuge) as soon as possible after collection. Following centrifugation, the resulting plasma will be transferred directly into plain plastic tubes. These samples will be stored at the clinical site at around -70°C using dry ice till transferred to the freezers area to be stored in the -70°C freezers. All plasma samples will be divided into two (2) aliquots. All samples will be collected into suitably labelled tubes (subject no., part one from study code, the year the study was assigned and the number of the study, study period, sample no. and aliquot no.).

5.12. Case Report Forms

The IPRC will supply Case Report Forms (CRFs). Case Report Forms must be completed for each subject enrolled in this study and will be reviewed at the end of each study period for completeness and acceptability by IPRC personnel at the study site.

5.13. Drug Bioanalysis

[redacted]

Incurred Sample Reanalysis

[redacted]

5.14. Quality Unit

The Quality Unit (QU) of IPRC will be responsible for the conduction of the study according to the GLP, ICH-GCP guidelines, the most recent revised version of the Declaration of Helsinki (Fortaleza, October 2013), the applicable regulatory requirement, the study protocol and the in-house SOP's, for both the clinical and analytical tasks. A complete audit is to be performed by the QU for the overall study execution. A final quality unit statement will be issued to indicate each audit task.

5.15. Data Quality Assurance

Monitoring details describing strategy, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Monitoring Plan.

Study monitor, designated by Sponsor will perform source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients 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 local applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 25 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.

5.16. Audit and on-site Inspection

Prior to the start of the study, the investigator is required to confirm his/her agreement to conduct the study in accordance with the protocol and to give access to all relevant data and records to UNITHER Pharmaceuticals monitors, auditors, and designated agents of UNITHER Pharmaceuticals, IRBs/IECs, and regulatory authorities as required.

If an inspection of the site is requested by a regulatory authority for this study, the investigator must inform UNITHER Pharmaceuticals and designated agents of UNITHER Pharmaceuticals (Monitor) immediately that this request has been made.

6. MANAGEMENT OF INTERCURRENT EVENTS

6.1. Deviation from Study Protocol for the individual subject

When significant deviation from the Study Protocol is deemed necessary for an individual subject, the Principal Investigator or any person assigned by him must contact the Sponsor. Such contact with the Sponsor will be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study. Any deviation from the Study Protocol will be authorized only for that one subject. A description of the deviation from the Clinical and the reason(s) for it will be recorded on the appropriate Case Report Form.

6.2. Adverse Events

Subjects will be monitored throughout confinement for adverse events to the study formulations and/or procedures. The Study Physician or a medically qualified designee will be on site till the end of confinement and on call for the end of the study. At the time of the last blood collection in each study period, each subject will be asked how he/she is feeling. The Study physician will evaluate the situation and take any necessary action. At the beginning of the second period, subjects will be questioned concerning unusual symptoms, which may have occurred after the previous administration of the study drug. The Study Physician or a qualified medical designee will evaluate drug-related symptoms of clinical significance before the next dose is administered. All adverse events and treatment administered will be recorded in the final report.

6.2.1. Adverse events/ serious adverse events/ adverse drug reaction[11]

- *Adverse event* (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), for example, symptom or disease temporarily associated with the use of a medicinal product, whether or not considered related to the medicinal product.

- *Serious Adverse Event* (SAE) is one that suggests a significant hazard, contraindication, side effect, or precaution. A serious adverse drug event includes any event that:
  -Results in death
  -Is life threatening
  -Requires patient hospitalization or prolongation of existing hospitalization.
  -Results in persistent or significant disability / incapacity (as per reporter's opinion)
  - Is a congenital anomaly / birth defect.
  -Or other seriousness beyond common definitions such as important medical events which might jeopardize the patient or require intervention to prevent the other outcomes as listed in other definitions of seriousness.

- *Adverse Drug Reaction* (ADR) is a response to a drug which is noxious and unintended, that occurs at doses normally used in man for prophylaxis, diagnosis, modification of a physiological function or therapy of a disease.

The Study Physician will determine in the course of the study whether any adverse events have occurred and will rate their intensity as follows:

Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; no intervention indicated

Moderate: minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental ADL

Severe or medically significant but not immediately life threatening: hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL

Life-threatening consequences: urgent intervention indicated

Death related to AE.

6.2.2. Relationship to the Test Drug

The Principal Investigator will judge whether or not, in his opinion, the adverse drug reaction was related with the drug. The study physician will decide if the adverse event is drug- related or not related. Nevertheless, the adverse event is to be recorded as follows:

Certain/related: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration and which concurrent disease or other drugs or chemicals cannot explain.

Probable/likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals and which follows a reasonable response on withdrawal (dechallenge).

Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: A clinical event, including laboratory test abnormality with a temporal relationship to drug administration which makes a causal relationship improbable and in which other drugs,

chemicals or underlying disease provide plausible explanation.

Unrelated: A clinical event, including laboratory test abnormality, which can be explained by any reason excluding the administered drug.

Not assessable/unclassified: A report suggesting an adverse event that cannot be judged because information is insufficient or contradictory and which cannot be supplemented or verified.

6.2.3. Adverse Event Documentation

The recording of every AE/ SAE has to meet the following requirement:

-Subject identification number and initials.
-Exact documentation of the event.
-Exact description of temporary sequence to the therapy course when experienced.
-Documentation of severity.
-Documentation of the results of diagnostic and therapeutic measurements.
-Results of repeated exposure if possible.
-Details of the development and outcome including medical assessment
-As much data as possible must be obtained which are important for the assessment concerning the relationship of the AE/SAE to study drug.
-Critical examination of the relationship to study drug.

6.2.4. Subjects' Adverse Events Form

Subject will be given an Adverse Events Form (in Arabic language) on Day 1 of each Study Period. Subjects will be asked for side effects, or unexpected events. Separate form will be used for each study period.

6.2.5. Reporting of adverse events or serious adverse events

[redacted]

[redacted]

6.2.6. Follow- up after adverse events

All adverse events and serious adverse events must be followed up until a conclusion is reached. Any subject withdrawn from the study due to any adverse event will be followed up until a conclusion is reached, also. This conclusion must be reported in the CRFs and to the Sponsor, in the event of an SAE.

6.3. Concurrent Medications

[redacted]

6.4. Modification of the Study Protocol

Neither the Principal Investigator, nor the Sponsor will modify this Study Protocol without first obtaining the concurrence of others. The modification must be documented in writing and signed by the Principal Investigator and the Sponsor. Any change in research activity, except for those necessary to remove an apparent immediate hazard to a subject, must be reviewed and approved by the IRB before implementation.

6.5. Subject Withdrawal

Each subject has the right to withdraw from the study at any time without jeopardy or prejudice. The Principal Investigator or the Study Physician may discontinue any subjects' participation when he feels it is necessary for any reason including adverse events or failure to comply with the study protocol. Should a subject withdraw from the study, the reasons must be stated on the Case Report Form and a final evaluation of the subject will be performed.

When a subject withdraws after having received the dose, he/she has to be informed by the principal investigator when he/she can take drugs again. This may become especially important when the subject withdraws for medical reasons, which may require drug therapy.

Furthermore, participation in this clinical study could be discontinued by the Principal Investigator or by the Sponsor for any of the following reasons:

- Adverse events;
- Significant protocol violation such as restrictions regarding alcohol and drug use, and non-respect of the fasting conditions;
- Difficulties with blood collection;
- Emesis following drug administration (subjects who experience emesis during the course of a bioequivalence study for immediate-release products, should be deleted from statistical analysis if vomiting occurs at or before 2 times median t_{max}).

The Principal Investigator can also remove a subject from the study if it is determined that the subject is uncooperative during the study. The Principal Investigator can remove a subject from the study due to an unanticipated event that could result in an inadequately characterized profile, such as missed blood draws, an adverse event such as diarrhea or a meal deviation. Details of reasons for removal of subjects will be recorded, reported to the Sponsor and documented in the final report.

6.6. Replacement of withdrawal subjects

If a subject is withdrawn before the first study drug administration, he/she will be replaced by the next qualifying alternate. The replacing alternate subject will receive the study products in the same sequence and under the same conditions as the dropped subject, and he/she will undergo the entire protocol procedure. Withdrawals after study drug administration will not be replaced.

When a subject is withdrawn from the study, the reasons are stated on the Case Report Form and a final evaluation of the subject will be performed.

7. DATA ANALYSIS

7.1. Pharmacokinetic Analysis[12,13]

Tramadol C_{max} and $AUC_{0\rightarrow t}$ are considered the *primary pharmacokinetic parameters*.

$AUC_{0\rightarrow t}$: The area under the plasma concentration versus time curve, from time (0) to the last measurable concentration (t), as calculated by the linear trapezoidal method.

$AUC_{0\rightarrow \infty}$: The area under the plasma concentration versus time curve from time (0) to infinity. $AUC_{0\rightarrow \infty}$ is calculated as the sum of the $AUC_{0\rightarrow t}$ plus the ratio of the last measurable plasma concentration to the elimination rate constant.

[redacted]

[redacted]

[redacted]

7.2. Statistical Analysis[14,15]

Samples from all subjects who complete the study will be analyzed for the plasma concentrations and considered for statistical analysis. Samples from withdrawals, if any, will be analyzed if the profile of at least one period can be determined. If necessary, an unequal number of subjects per sequence will be used.

The pharmacokinetic results from withdrawals who do not provide evaluable data for both the test and reference products will not be included in statistical evaluation. Concentration data and pharmacokinetic parameters from such subjects will be presented in the individual listings but will not be included in the summary statistics.

[redacted]

[redacted]

[redacted]

7.2.1. Descriptive statistics

Descriptive statistics, including the means, standard deviations, standard error of the mean and coefficient of variation, shall be reported for the plasma concentrations. For pharmacokinetic parameters, arithmetic means, standard deviations, standard error of the mean, minimum, median, maximum, coefficient of variation and geometric mean shall be reported.

[redacted]

[redacted]erm.

7.2.3. Confidence Intervals and Bioequivalence Evaluation

Consistent with the two one-sided tests for bioequivalence, 90% confidence intervals for the [redacted]

[redacted]

7.2.4. Sample Size Calculation

[redacted]

8. FINAL REPORT, SUPPLEMENTARY DOCUMENTATION AND PUBLICATION POLICY

Final Report: All reporting will be performed by IPRC. The final report will address all aspects of the study and will include the interpretation of all relevant data and any conclusions from them[16]. A copy from the final report shall be reserved by IPRC after the completion the study. A sample informed consent form, a sample CRF, a copy of the IRB approval, the bioanalytical report including method validation report and 20% chromatograms will be appended to the final report. The subjects' CRFs, clinical laboratory tests, standard calibration curves and quality control samples shall be supplemented on request. The final report shall be signed by the IPRC Investigator(s) and submitted to the sponsor with the other study supplements[17].

Source Documents: Source documents include original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, accountability records, recorded data from automated instruments, informed consent forms, case report forms, bioanalytical results and chromatograms, pharmacokinetic spreadsheets, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilms or magnetic media, x-rays, subject files, and records kept at any department involved in the trial). All *Source Documents* generated in connection with this study will be retained in the limited access file storage area of IPRC, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents shall be handled, stored and archived according to in-house procedures to assure for accurate reporting, interpretation and verification, under the supervision of the QU.

Publication Policy: All information concerning Test product and the Sponsor operations, such as patent applications, formulae, manufacturing processes, basic scientific data or formulation information, supplied by Sponsor and not previously published is considered confidential by the Principal Investigator and the Study Director. The results of this study are UNITHER Pharmaceuticals proprietary and cannot be published or presented in any scientific meeting without any agreement from the sponsor.

9. REFERENCE

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4 Guidance on Good Clinical Practice (CPMP/ICH/135/95), ICH Topic E 6 (R2), the European Medicines Agency (EMA), June 2017.

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6 Guidelines for the conduct of Research involving Human subjects at the National Institutes of Health. Office of Human Subjects Research (OHRP), Title 45, Part 46 Protection Of Human Subjects

Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html.

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https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf

8 Guideline On The Investigation Of Bioequivalence. Committee For Medicinal Products For Human Use (CHMP), European Medicines Agency (EMA), Doc. Ref.: CPMP/EWP/QWP/1401/98 Rev. 1/ Corr, London, 20 January 2010.

Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf

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[10] The European Medicines Agency (EMA). Guideline on bioanalytical method validation, EMEA/CHMP/EWP/192217/2009, Committee for Medicinal Products for Human Use (CHMP), 1 February 2012.

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[11] Note for Guidance on Clinical Safety Data Management; Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95), ICH Topic E 2 A, The European Medicines Agency (EMA), June 1995.

Available at:
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf

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[redacted]

[14] Guidance for Industry: Statistical Approaches to Establish Bioequivalence. US Dept. of Health and Human Services, Food and Drug Administration (FDA), Centre for Drug Evaluation and Research (CDER), January, 2001.

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[15] Note For Guidance On Statistical Principles For Clinical Trials (CPMP/ICH/363/96), ICH Topic E 9, The European Medicines Agency (EMA). September 1998.

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[16] Note for Guidance on the Structure And Content Of Clinical Study Report (CPMP/ICH/137/95), ICH Topic E 3, The European Medicines Agency (EMA). July 1996.

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10. Protocol Version History and Summary of Changes

Version	Description of change	Change carried out on pages	Reason of Change
1.0	creation	NA	NA

ANNEXES

[redacted]

ANNEX VI PROTOCOL ADMINISTRATIVE CHANGES

COMPARATIVE RANDOMIZED, SINGLE DOSE, TWO-WAY CROSSOVER OPEN LABEL STUDY TO DETERMINE THE BIOEQUIVALENCE *OF 5 MG/ML TRAMADOL HYDROCHLORIDE ORAL SOLUTION (08P1902F0)* RELATIVE TO *CONTRAMAL® 100 MG/ML ORAL SOLUTION* AFTER AN ORAL ADMINISTRATION TO HEALTHY ADULTS UNDER FASTING CONDITIONS