Pharmacokinetic study of a Fixed Drug Combination nefopam hydrochloride (30 mg) / paracetamol (500 mg) and individual nefopam hydrochloride and paracetamol taken alone or concomitantly after oral single dose.

An open-label, randomized, four-period, four treatments, cross-over trial in healthy volunteers

Clinical study protocol: UP-CLI-2019-001

Accutest reference ARL/20/277

Version 02 – 28 June 2021

Sponsor	**UNITHER Pharmaceuticals** 3-5 Rue Saint-Georges 75009 Paris France
Test product	30 mg nefopam hydrochloride / 500 mg paracetamol Fixed Dose Combination (FDC) (Compound number: 08P1737F0)
Development Phase	Pharmacokinetic study
EudraCT number	2019-002753-37
Study Center	Accutest Research Laboratories (I) Pvt. Ltd., A-31, M.I.D.C, T.T.C Industrial Area Khairane, Navi Mumbai –400709, Maharashtra, INDIA. Tel: + 91 22 2778 0718/19/21 Fax: + 91 22 2778 0720

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE(s)	Adverse Event(s)
ANOVA	Analysis of Variance
ARL	Accutest Research Laboratories (I) Pvt. Ltd.
ATC	Anatomical Therapeutic Chemical
AUC_{0-t}	Area Under The Concentration Versus Time Curve Up To The Last Measurable Time Point
AUC_{0-inf}	Area Under The Concentration Versus Time Curve From Time 0 To Infinity
BA	Bioavailability
BE	Bioequivalence
β-hCG	Serum Beta Human Chorionic Gonadotropin
BLQ	Below the Limit of Quantification
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CHO	Carbohydrate
CI	Confidence Interval
CIOMS	Council for International Organizations of Medical Sciences
cm	Centimeter (s)
cc	Cubic Centimeter
C_{max}	Maximum Observed Drug Concentration In Plasma
COA	Certificate of analysis
COVID-19	Corona Virus Disease of 2019
CRF	Case Report Form
CS	Clinically Significant
CV	Coefficient of Variation
CYP	CYP450 enzymes
°C	Degree Celsius
dL	Deciliter
EC	Ethics Committee
ECG	Electrocardiogram
°F	Degree Fahrenheit
FDC	Fixed Drug Combination
g	Grams
GABA	Gamma-Aminobutyric acid
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
Hb	Haemoglobin In Blood
HBsAg	Hepatitis B Surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immuno Deficiency Virus
hpf	High power field
hr(s)	Hour(s)
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
ICF	Informed Consent Form
IP	Investigational Product
IMP	Investigational Medicinal Product
INR	International Normalised Ratio
IU	International Unit

IUD	Intrauterine device
IUS	Intrauterine system
i.v.	Intravenous
K_{el}	Elimination Rate Constant
Kcal	Kilocalorie
kg	Kilogram(s)
L	Liter
LC-MS/MS	Liquid Chromatography-Mass Spectrometry/Mass Spectrometry
LSM	Least Square Mean
m	Meter
mg	Milligram
mL	Milliliter
mm	Millimeter
mM	Millimolar
µg	Microgram
µL	Micro liter
µm	Micrometer
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MSV	Missing Sample Values
NA	Not Applicable
NAPQI	N-acetyl-p-benzoquinoneimine
NCS	Not Clinically Significant
ng	Nanogram
No.	Number
NRV	Not-reportable Value
PBS	Pharmacokinetic and Biostatistics
PCV	Packed Cell Volume
pg	Picogram
PI	Principal Investigator
PROC GLM	Procedure General Linear Model
PK	Pharmacokinetic
QA	Quality Assurance
QAU	Quality Assurance Unit
RBC	Red Blood Cell
RPM	Revolutions per minute
SAE(s)	Serious Adverse Event(s)
SAS	Statistical Analysis System
SD	Standard Deviation
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SOC	System Organ Classification
SOP(s)	Standard Operating Procedure(s)
$t_{1/2}$	Terminal Half-Life
T_{max}	Time To Observe Maximum Drug Concentration In Plasma
tbsp	Tablespoon
tsp	Teaspoon
ULN	Upper limit of normal
U/L	Units per liter
WBC	White Blood Cell
WMA	World Medical Association

GENERAL INFORMATION

Name and Address of the Sponsor	
Sponsor's Authorized Signatories:	
[redacted] **Address: UNITHER Pharmaceuticals.,** 3-5 rue Saint Georges 75009 PARIS FRANCE	
NAME AND ADDRESS OF THE STUDY PERSONNEL	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

*Being a registered medical doctor, responsibilities of Clinical Investigator will be handled by Principal Investigator (PI).

INSTITUTIONS INVOLVED IN THE STUDY

INVESTIGATOR'S STATEMENT

I recognize that all information concerning this study and the medication provided by the sponsor may not be previously published and is confidential information.

I accept that the sponsor and the Ethics Committee must approve the protocol and subsequent changes to the protocol in writing before its implementation (except where it is necessary to eliminate immediate hazards to participating subjects or when such changes may involve only administrative aspects of the study).

I hereby give my consent to conduct the study in accordance with this protocol. I agree to comply with all requirements of the current version of the Declaration of Helsinki, the current ICH GCP, New Drugs and Clinical Trials Rules 2019 G.S.R. 227® and EMA regulatory guidelines as well National Laws and Regulations. I agree to comply with all relevant SOPs required for the conduct of this study and further agree to ensure that all associates assisting in the conduct of study are informed regarding their obligations.

SPONSOR'S STATEMENT

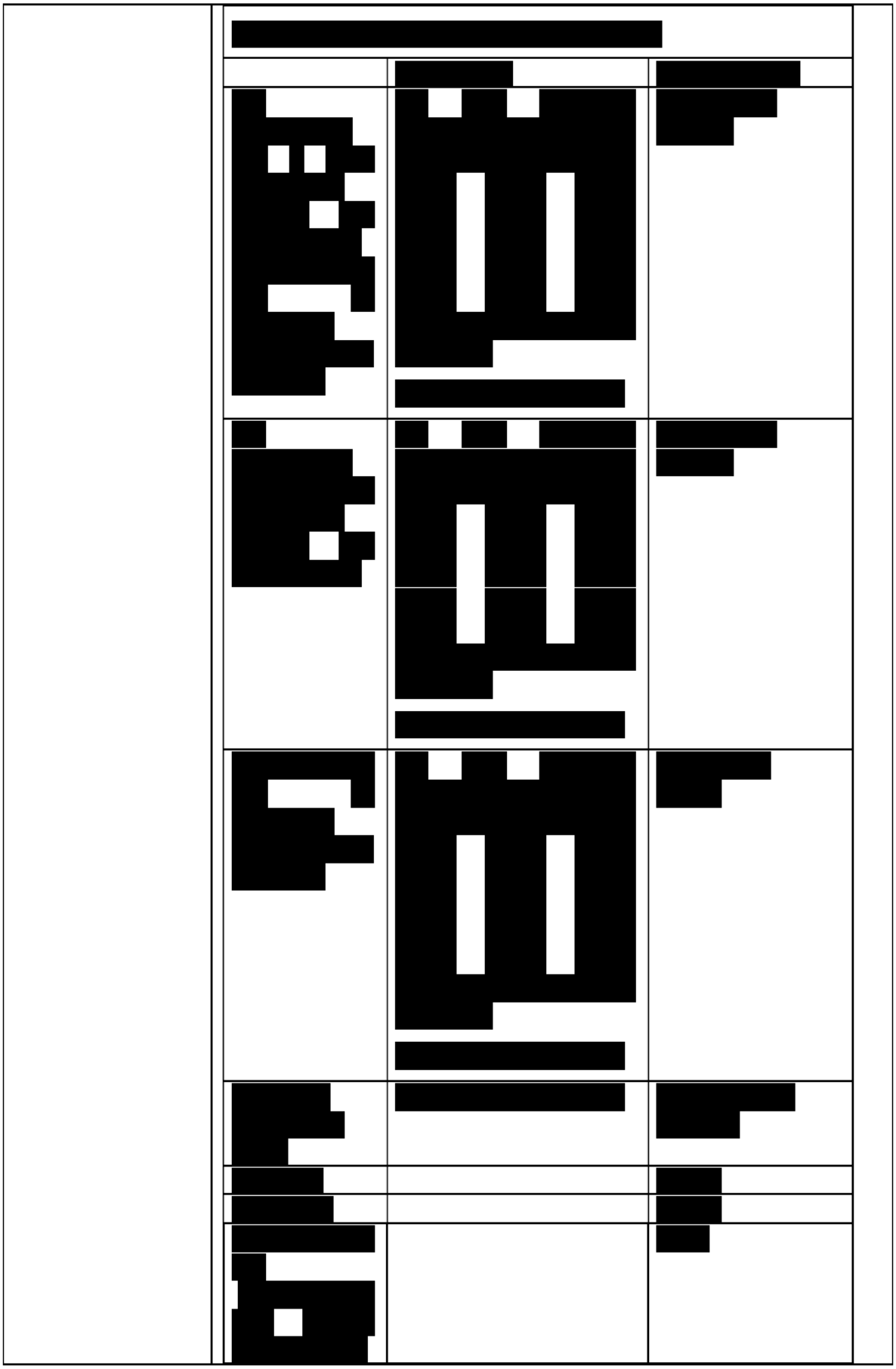
I, on behalf of **UNITHER-Pharmaceuticals.,** have read, understood and approved this protocol. I hereby give my consent to conduct the study in accordance with this protocol. I agree to comply with all requirements regarding the obligations of sponsor and all other pertinent requirements of the current version of the Declaration of Helsinki, the current ICH GCP, New Drugs and Clinical Trials Rules 2019 G.S.R. 227 (E) and EMA regulatory guidelines as well as relevant National Laws and Regulations.

PROTOCOL SYNOPSIS

Title	Pharmacokinetic study of a Fixed Drug Combination (FDC) nefopam hydrochloride (30 mg) / paracetamol (500 mg) and individual nefopam hydrochloride and paracetamol taken alone or concomitantly after oral single dose. An open-label, randomized, four-period, four treatments, cross-over trial in healthy volunteers
Background	[redacted]
Study Design	A Randomized, Open Label, Balanced, Four Treatment, Four Period, Four Sequence, Single Dose, Crossover Design.
Objectives	The primary objective of this study is to evaluate the pharmacokinetic parameters concentration $(C°)_{max}$ and Area Under the Curve $(AUC)_{last}$ for nefopam hydrochloride and paracetamol when administrated alone and as part as combination after oral single dose. The secondary objectives are: - To evaluate the potential drug-drug interactions between nefopam hydrochloride and paracetamol when administered concomitantly, or alone after oral single dose. - To evaluate the bioequivalence between the Fixed Drug Combination (FDC) nefopam hydrochloride (30 mg) / paracetamol (500 mg) and individual nefopam hydrochloride and paracetamol taken concomitantly after oral single dose. - to assess other pharmacokinetic (PK) parameters obtained for nefopam hydrochloride and paracetamol when administrated alone or as part as combination. - to evaluate the pharmacokinetic profiles of N-desmethyl-nefopam (active metabolite of nefopam per os). - [redacted] to evaluate the safety/tolerability of both drugs when administered separately, concomitantly or combined based on adverse events reported after treatment .
No. of Subjects	A total of 32, (16 (±5) males and 16 (± 5) females) healthy, adult human volunteers will be enrolled.

Assessment of Subjects	On Screening day Breath alcohol test, demographic data, medical / clinical history, physical examination including vital signs, 12-lead Electrocardiogram (ECG), chest X-ray (P/A view) (if required based on any significant past medical history and/or positive finding in respiratory system examination), haemogram, biochemistry, serology (HIV, Hepatitis B and C) and urinalysis will be performed. **Note:** Due to ongoing COVID-19 pandemic, the subjects will undergo pre-screening activities in accordance with the SOP titled "Handling of pre-screening activities during COVID-19 pandemic." The subjects will also sign the IEC approved additional subject information sheet and informed consent form for undergoing pre-screening activities and follow general safety instructions during COVID-19 pandemic. A. On Check-in day: Breath alcohol test, relevant medical / clinical history, physical examination including vital signs, Urine screen for drug abuse for commonly abused substances, serum pregnancy test for female subjects will be done. B. During Confinement Period: Well-being assessment and vital signs measurement. C. At check-out Well-being assessment, physical examination, measurement of blood pressure, pulse rate, respiration rate and body temperature. D. Post Study Evaluation: Well-being assessment, physical examination (including vital signs), haemogram, biochemistry and urinalysis will be performed. **Note:** 1. Well-being assessment and breath alcohol analysis will be done during subject's visit for follow-up and ambulatory PK samples if applicable. 2. Any other assessment including laboratory test(s) will be done if judged necessary by the PI/Sub-investigator/Co-investigator person at any time during the course of study.
Restrictions	[redacted]

	[redacted]
Meals	[redacted]
Dose Administration	Single oral dose of Investigational medicinal product either of test product (T) or reference product (R1), (R2) and (R3) in sitting position in each period, after an overnight fast of at least 10.00 hrs as per the randomization schedule.
Washout	The successive study periods will be separated by at least 06 calendar days.
Housing	Subjects will be housed for at least 10.50 hrs prior to dosing and up to 24.00 hrs post-dose.
Study Duration	The duration of the clinical phase will be approximately 22 days.
Blood Sample Collection	**For Paracetamol and it main metabolites (Sulfate and Glucuronide) and Nefopam and its metabolite (N-desmethyl-nefopam):** [redacted] **For Paracetamol and its main metabolites (Sulfate and Glucuronide):** [redacted] **For Nefopam and its metabolite (N-desmethyl-nefopam): 4 ml each (20 samples):** [redacted]



	[redacted]
Total blood loss	[redacted]
[redacted]	[redacted]
Note	***All activities related to handling of investigational medicinal products, dosing, blood sample collection, sample handling, processing and sample analysis will be carried out under sodium vapour light.***
Analytical Method	Nefopam, Paracetamol, its main metabolites (Sulfate and Glucuronide), N-desmethyl-nefopam, in plasma will be quantified using a validated analytical method.
Pharmacokinetic Parameters Evaluated	The following PK parameters will be analyzed: **Primary:** C_{max} and AUC_{0-t} **Secondary:** AUC_{0-inf}, AUC_{0-t}/AUC_{0-inf}, Residual area, T_{max}, K_{el} and $t_{1/2}$
Statistical Evaluation	Pharmacokinetic and Statistical analysis will be done using SAS® 9.4 version. [redacted]

[redacted]

For Profiling only:

[redacted]

Ethical consideration	Study will be conducted as per ethical considerations. Details are mentioned in section 11.0 1. Risk and Benefits 2. Ethics committee review and communications 3. Informed Consent Process 4. Confidentiality and Ownership of Data and Coding Procedure

1.0 BACKGROUND INFORMATION:

1.1 Disease and context

The International Association for the Study of Pain defines pain as an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. Pain is a major health problem that substantially alters quality of life. Treatment of pain is a challenge in clinical practice as not all patients respond sufficiently to available treatments and the burden of adverse reactions may be high. It is a complex process involving interactions between peripheral and central nervous system pathways with various neurobiological mechanisms being involved. Pain is always subjective and remains the leading cause of physician consultations.

Acute pain is considered adaptive, in that it has a warning function. It is of short duration (generally up to a few weeks) and declines with the healing of the underlying injury or disease (e.g. post-surgical pain).

1.2 Treatment of pain

The World Health Organization (WHO) created – initially for cancer pain relief in adults - a three-step ladder ("pain ladder" or analgesic ladder). This ladder, proposing therapeutic strategy in pain control, is now widely used by medical professionals as a guideline for the use of drugs in the management of all types of pain.

The WHO's therapeutic strategy relies upon the concurrent and sequential use of a series of treatment procedures, which must be adapted to the needs of the individual patient. For patients with mild pain, the recommendation is to use a non-opioid drug, such as aspirin, paracetamol, or any of the non-steroidal anti-inflammatory drugs. If, in the recommended dosage and frequency, this is not effective in relieving the pain (patients with moderately severe pain) a drug such as codeine or an alternative weak opioid should be added to the given medication. When a weak opioid drug in combination with a non-opioid drug fails to relieve the pain (patients with severe pain) a strong opioid, such as morphine should be used. Adjuvant drugs should be added to the opioid and non-opioid drugs, if required for specific indications.

According to this WHO's recommendation, also supported by guidelines on the management of moderate to severe pain released by the French National Agency for the Safety of Medicines and Health Product (ANSM), treatment of moderate pain can be achieved with a combination of a weak opioid and a non-opioid.

[redacted]

1.3 Rational for nefopam/paracetamol as a Fixed Dose Combination (FDC)

[redacted]

1.4 Non-Clinical and Clinical Information

[redacted]

1.5 Rationale of the study

[redacted]

The aim in developing an oral fixed dose combination (FDC) of 30 mg nefopam hydrochloride and 500 mg paracetamol to relieve moderate to severe pain is to fill the gap in the therapeutic armamentarium of pain management, using a new non-opioid combination product.

[redacted]

[redacted]

1.6 Investigational Drug

1.6.1 Investigational Medicinal Products

Test Product (T): Fixed Drug Combination (FDC) Nefopam Hydrochloride (30 mg)/Paracetamol (500 mg) Tablets X 2

Reference Product (R1): Paracetamol 500 mg per os (Panadol® 500mg tablet) X 2+Nefopam 30 mg per os (Acupan® 30mg Tablets) X 2

Reference Product (R2): Nefopam 30 mg per os (Acupan® 30mg tablet) X 2

Reference Product (R3): Paracetamol 500 mg per os (Panadol®500mg tablet) X 2

1.6.2 General Pharmacology [7]

Code of investigational medicinal product: FDC 08P1737F0

Active substances: nefopam hydrochloride and paracetamol

Dosage form and presentation: immediate release oral FDC tablet with 30 mg nefopam hydrochloride and 500 mg paracetamol

Composition: Physicochemical properties of the two active ingredients are presented in Table.

Table: Chemical characteristics of FDC 08P1737F0

Name	Nefopam hydrochloride	Paracetamol
[redacted]		

Mechanism of Action:

For Nefopam

Pharmacotherapeutic group: pharmaceutical products with analgesic properties only, Anatomical Therapeutic Chemical (ATC) code: N02BG06

[redacted]

***Pharmacodynamic effects**:*

Nefopam is an analgesic. Nefopam stimulates the descending serotonergic pathways modulating pain. It inhibits the reabsorption of synaptosomal neurotransmitters, noradrenalin, dopamine, 5-hydroxytryptophan and gamma-Aminobutyric acid (GABA). It stimulates the release of dopamine and GABA in the brain.

[redacted]

For Paracetamol

Pharmacotherapeutic group: Analgesics, Anilides, ATC code: N02BE01

[redacted]

Indication and Usage:

Symptomatic treatment of fever and pain.

Pharmacokinetics properties

For Nefopam

Absorption: [redacted]

Biotransformation: [redacted]

Elimination: [redacted]

For Paracetamol

Paracetamol is readily absorbed following oral and rectal administration.

Bioavailability is slightly lower following rectal use, compared with oral use.

Absorption is slower and dependent on the duration of contact with the mucosa.

Peak plasma concentrations measured following administration of 1 g paracetamol are as follows: tablets: up to 17 mg/L; suppositories: up to 7 mg/L. Plasma concentrations are approximately half, following a dose of 0.5 g. Peak plasma concentration is reached approximately 1 hour after dosing for the tablets, ½ an hour after dosing for the effervescent tablets, and approximately 3 hours after administration for suppositories. At the therapeutic doses, protein binding rate is relatively low (approximately 10%) and is higher at toxic doses (15 to 21%). Bioavailability is approximately 90% for doses over 1 g and more than 60% for the lowest doses.

The half-life ranges from 2 to 3 hours in adults at the therapeutic doses. It is slightly shorter in children, but longer in the elderly.

Paracetamol is metabolised by the liver, and its metabolites are mainly excreted via the urine: up to 98% in 24 hours, predominantly in glucuronide and sulfate form.

In case of overdose, part of the paracetamol is metabolised via biochemical pathways into catecholamine derivatives or cysteine conjugates. An intermediate product is thus created: an epoxide or similar radical thought to be the cause of hepatotoxicity.

1.6.3 Adverse Effects [6]

[redacted]

- Very common (≥1/10);
- Common (≥1/100 to <1/10);
- Uncommon (≥1/1,000 to <1/100);
- Rare (≥1/10,000 to <1/1,000);
- Very rare (<1/10,000).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

For Nefopam

Table: Undesirable effects of nefopam

	Very common	**Common**	**Rare**	**Undetermined frequency**
Psychiatric disorders			Excitability* Irritability*Hallucination Abuse** Drug-dependence**	Confusionnal state
Nervous system disorders	Drowsiness	Dizziness* Light-headedness Paraesthesia Tremor	Convulsions* Confusion Postoperative confusion Insomnia Headache	Coma
Vascular disorders		Tachycardia* Palpitations* Hypotension	Syncope`	
Gastrointestinal disorders	Nausea with or without vomiting	Dry mouth* Abdominal pain Diarrhoea		
Renal and urinary disorders		Urinary retention	Decrease renal function Harmless pink discolouration of the urine	
Eye disorders			Blurred vision	
Immune system, skin and subcutaneous tissue disorders	Sweating*	Allergic reactions	Postoperative hypersensitivity (angioedema, anaphylactic shock) Pruritus Erythema Urticaria Faintness	

*Although never reported, other atropine effects than those described are likely to be observed.
**According to the PRAC conclusions, the suggested plausible mechanism is the inhibition of dopamine recapture.

For Paracetamol

Paracetamol tablets cause few undesirable effects, providing the treatment duration and dose are followed.

Table: Undesirable effects of paracetamol

	Very rare	**Undetermined Frequency**
Blood and lymphatic system disorders	Thrombocytopenia	In patients with glucose-6-phosphatedehydrogenase [G6PD] deficiency, haemolytic anaemia is not excluded
Immune system disorders	Cutaneous reactions including erythema, urticaria, angioedema and other signs of anaphylaxis, and Stevens-Johnson syndrome	
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin or other NSAIDs	
Hepatobiliary disorders	Hepatic dysfunction	
Skin and subcutaneous tissue disorders	Very rare cases of severe skin reactions have been reported	

If these phenomena develop, patients should stop treatment and see a doctor immediately.

[redacted]

1.6.4 Contraindications and Drug Interactions [6]

Contraindications:

For Nefopam

[redacted]

For Paracetamol

The contraindications of paracetamol are:

- Hypersensitivity to the active substance, phenacetin or to any of the excipients listed.
- Serious hepatic impairment.

- Repeated administration of paracetamol is contraindicated in patients with anaemia, heart disease or lung disease.

Drug Interactions:

For Nefopam

Use of Nefopam with other substances with an anticholinergic or sympathomimetic activity may give rise to additive effects.

It should be noted that many medicinal products or substances can have additive depressant effects on the central nervous system and contribute to a decrease in alertness. These include morphine derivatives (analgesics, cough suppressants and replacement therapies), neuroleptics, barbiturates, benzodiazepines, non-benzodiazepine anxiolytics (such as meprobamate), hypnotics, sedative antidepressants (amitriptyline, doxepin, mianserin, mirtazapine, trimipramine), sedative H1- antihistamines, centrally-acting antihypertensives and baclofen.

Nefopam may interfere with certain tests for benzodiazepines and opioids. These tests may yield false-positive results in patients taking Nefopam.

The intensity and incidence of adverse reactions increase when nefopam is co-administered with codeine, pentazocine or dextropropoxyphene.

Nefopam is intensively metabolised. However, as the enzyme responsible for the biotransformation of nefopam is not known, potential interactions with CYP450 enzymes (CYP) inhibitors/inducers cannot be anticipated. Caution should therefore be exercised whenever nefopam is co administered with a CYP inhibitor/inducer.

The known hepatotoxicity of paracetamol, observed in dogs given very high doses of paracetamol, was exacerbated when very high doses of nefopam were administered. These studies showed that oral doses of paracetamol 236 mg/kg/day and nefopam 24 mg/kg/day potentiate the hepatotoxicity of paracetamol. These doses are approximately six to eight times higher than the average dose in humans. Lower doses, equivalent to three or four times the human dose have not given rise to potentiation of hepatotoxicity.

For Paracetamol

- Administration of activated charcoal reduces the absorption of paracetamol following
- overdose.
- Liver enzyme inducers (such as barbiturates, Diphantoine) and alcohol may increase the hepatotoxicity of paracetamol.
- The half-life of chloramphenicol may be extended by 2 to 3 hours up to 18 to 24 hours in the event of concomitant administration of paracetamol.
- As paracetamol is weakly bound to plasma proteins, it may be used concomitantly with anticoagulants. However, use of paracetamol for several days may increase the risk of bleeding. In this case, regular monitoring of the International Normalised Ratio (INR) is recommended.
- Due to the risk of decreased leukocyte count (leukopenia) during concomitant
- administration of paracetamol and AZT (zidovudine), simultaneous administration should only take place on medical advice.

- The absorption of paracetamol may increase when co-administered with metoclopramide and decrease when co-administered with cholestyramine.
- Concomitant administration of diflunisal increases serum paracetamol concentrations. Elevated serum paracetamol concentrations have been associated with hepatotoxicity.

1.7 Rationale of Dose [6]

[redacted]

1.8 Study Conduct

This study will be conducted in compliance with the protocol approved by the Ethical Committee (EC) and according to Good Clinical Practice (GCP) standards. Deviation having any impact on the safety of the subject or on study data will not be implemented without prior review and approval of the EC except where it may be necessary to eliminate an immediate risk to a study subject. In such a case, the deviation will be reported to the EC as soon as possible.

2.0 STUDY OBJECTIVE

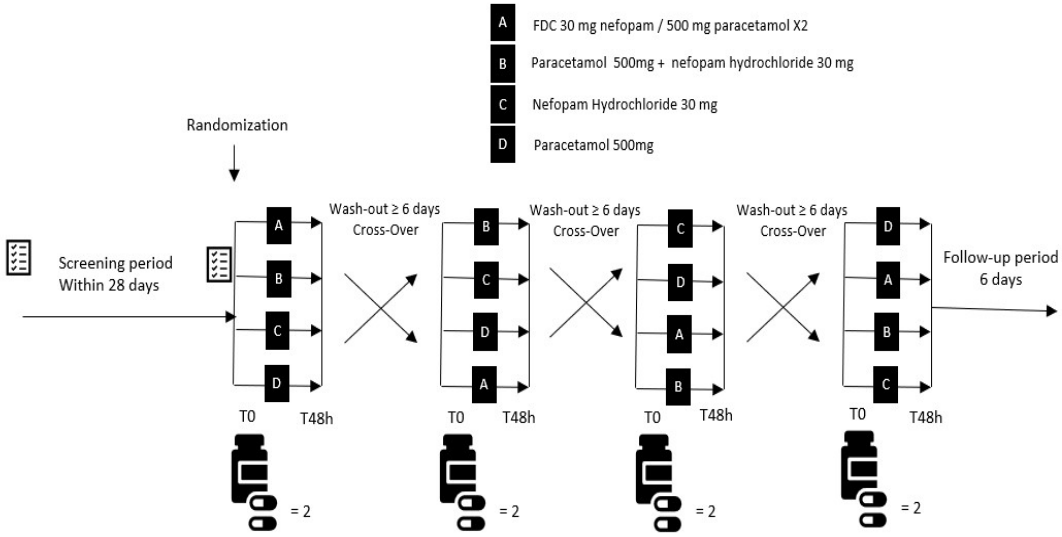
The primary objective of this study is to evaluate the pharmacokinetic parameters concentration $(C°)_{max}$ and Area Under the Curve $(AUC)_{last}$ for nefopam hydrochloride and paracetamol when administrated alone or as part as combination after oral single dose.

The secondary objectives are:

- [redacted]
- to assess other pharmacokinetic (PK) parameters obtained for nefopam hydrochloride and paracetamol when administrated alone or as part as combination.

- to evaluate the pharmacokinetic profiles of N-desmethyl-nefopam (active metabolite of nefopam per os)
- [redacted]
- to evaluate the safety/tolerability of both drugs when administered separately, concomitantly or combined based on adverse events reported after treatment.

3.0 STUDY DESIGN AND STUDY RATIONALE



Discussion of the Study Design

[redacted]

v. [redacted]

Following precautions are incorporated into the study to minimize bias:

i. Volunteers are sequentially assigned to randomly ordered treatment.

ii. Volunteer enrollment is dependent on satisfactory fulfillment of the given list of inclusion and exclusion criteria.

iii. The circumstances when individual volunteers withdraw prior to plan completion of the study are specified.

iv. The analyst will be kept blind in respect to the treatments during the analysis.

Study Rationale

[redacted]

[redacted]

3.1 Generation and handling of Randomization

The randomization for this study will be generated by PBS personnel using the PROC PLAN on statistical software SAS® 9.4 version. The handling of randomization will be done as per the SOP: Randomization of treatment.

The analyst concerned will be blinded to the sequence of administration of Test and Reference product to the individual subject.

3.2 Study Treatment

Test Product (T): Fixed Drug Combination (FDC) Nefopam Hydrochloride (30 mg)/Paracetamol (500 mg) Tablets X 2
Each FDC tablet contains nefopam hydrochloride 30 mg / paracetamol 500 mg.
Manufactured by: Unither Industrie, 17 Avenue des Portes Occitanes, 03800 Gannat, FRANCE
Dosage Form: FDC Tablet
Formulation strength: Nefopam Hydrochloride (30 mg)/Paracetamol (500 mg).
Dose: Nefopam Hydrochloride (30 mg)/Paracetamol (500 mg) X 2 FDC Tablets.

Reference Product (R1): Paracetamol 500 mg per os (Panadol® 500mg tablet) X 2 + Nefopam 30 mg per os (Acupan® 30mg Tablets) X 2
Each tablet contains nefopam hydrochloride 30 mg + Each tablet contains paracetamol 500 mg.
[redacted]
Formulation strength: 30 mg
Dosage Form: Tablet
Dose: 2 Tablets
+
[redacted]
Dosage Form: Tablet
Formulation strength: 500 mg
Dose: 2 Tablets

Reference Product (R2): Nefopam 30 mg per os (Acupan® 30mg tablet) X 2
[redacted]
Dosage Form: Tablet

Formulation strength: 30 mg
Dose: 2 Tablets

Reference Product (R3): Paracetamol 500 mg per os (Panadol® 500mg tablet) X 2
[redacted]

Dosage Form: Tablet
Formulation strength: 500 mg
Dose: 2 Tablets

3.3 Study Duration

Excluding screening period, the duration of clinical phase will be approximately 22 days including a washout period of at least 6 days for each study period.

Housing:
The subject will be housed from at least 10.50 hrs before dosing until 24.00 hrs post dose in the centre for each study period. Activities beyond 24.00 hrs will be conducted on ambulatory basis.

Visits:
Each eligible subject is required to return to the study centre on check-in days of each study period and ambulatory blood sample (s) collection.

3.4 Discontinuation / Termination of the Study

If the PI terminates or suspends the study without prior agreement of the sponsor, the PI will promptly inform the sponsor and the EC and will provide them with a detailed written explanation of the termination or suspension.

If the study is prematurely terminated or suspended by the sponsor, the sponsor will promptly inform the PI and the regulatory authority-(ies) of the termination or suspension and the reason(s) for the termination or suspension. The EC will also be informed promptly and will be provided with the reason(s) for the termination or suspension by the sponsor or by the PI.

[redacted]

3.5 Investigational Medicinal Product Accountability

3.5.1 Receipt

The IMPs will be accepted in accordance with current version of the Standard Operating Procedure (SOP) for 'Handling of Investigational Medicinal Product'. The Pharmacist will check the IMPs for integrity and correctness of the label. The

products will be accompanied by the certificate of analysis (COA). The sponsor will be responsible for the supply of IMPs in a properly labeled pack according to the requirements of Good Manufacturing Practice (GMP). The quantity of IMPs should be sufficient as per current version of the SOP for 'Handling of Investigational Medicinal Product' or as provided by the sponsor.

The drug content of the test product should not differ from that of the reference product by more than 5 percent

3.5.2 Storage and Dispensing

The investigational medicinal products will be stored under appropriate storage conditions as specified in the product label and/or as recommended by the sponsor in the securely locked pharmacy accessible only to authorized persons. The pharmacist will prepare the labels for the IMP dispensing vials/containers in accordance with the current version of the SOP. Labels should be approved by Quality Assurance (QA) prior to dispensing. The Pharmacist will carry out dispensing as per randomization code in accordance with the current version of the SOP for 'Dispensing of Investigational Medicinal Products' in presence of QA personnel.

3.5.3 Reconciliation

The PI will not allow the study drugs to be used for the purposes other than those indicated in this protocol. At the end of last dosing, the IMPs received, the quantity used for dispensing for the concerned study, the retention quantity and the balance quantity will be recorded in accordance with the current version of SOP 'Handling of Investigational Medicinal Product'.

3.5.4 Retention

The IMPs for the test and reference formulations will be retained as per the current version of the SOP for 'Handling of Investigational Medicinal Product'. The disposal of the retained samples will be done only at the end of the retention period as mentioned in the "IMP log" after obtaining written confirmation from the sponsor.

4.0 SELECTION AND WITHDRAWAL OF SUBJECTS

The subjects will be assessed for various inclusion/exclusion criteria mentioned below:

4.1 Inclusion Criteria

1. Male and non-pregnant female human subjects, age in the range of 18 – 45 years both inclusive.
2. Body Mass Index between 18.5-30 Kg / m^2 extremes included.
3. Subjects with normal findings [redacted]
4. Subjects with clinically acceptable findings [redacted]

[redacted]

4.2 Exclusion Criteria

1. Known history of hypersensitivity to Nefopam, Paracetamol or related drugs.
2. Requiring medication for any ailment having enzyme-modifying activity in the previous 28 days, prior to dosing day.
3. Subjects with a history of convulsive disorders.
4. Subject with a moderate or severe renal impairment (Glomerular Filtration rate below 60ml/min).
5. [redacted]

[redacted]

[redacted].

4.3 Precautions while enrolling females of childbearing potential:

Women of childbearing potential are females who have experienced menarche and do not meet the criteria for "women not of childbearing potential. "Women Not of childbearing potential are females who are permanently sterile or postmenopausal. Postmenopausal is defined as 12 consecutive months with no menses without an alternative medical cause.

Highly effective methods of contraception include hormonal contraceptives (e.g. combined oral contraceptives, patch, vaginal ring, injectables, and implants); intrauterine device (IUD) or intrauterine system (IUS); vasectomy of male partner and tubal ligation. Effective methods of contraception include barrier methods of contraception (e.g. male condom, female condom, cervical cap, diaphragm, contraceptive sponge). The allowed methods of contraception are only effective when used consistently, correctly and in accordance with the product label.

The possibility of known or unknown drug interactions between the hormonal contraceptives and the therapeutic product under investigation always exist. Moreover, there is a possibility that the therapeutic product under investigation may lessen the effectiveness of a hormonal contraceptive agent. Hence female subjects with child bearing potential using hormonal contraceptives will not be included in the study. However, following contraceptive methods will be acceptable if followed from the day of screening up to the completion of the study. The Investigator will ensure the appropriate usage of acceptable contraceptive methods by the subjects.

1. Non hormonal intrauterine device (IUD)
2. Non hormonal intrauterine system (IUS)
3. Vasectomy of male partner
4. Tubal ligation
5. Double barrier methods of contraception such as male condom, female condom, cervical cap, diaphragm, contraceptive sponge with spermicidal foam, gel, film, cream, or suppository are acceptable.

4.4 Timings of assessment of inclusion/exclusion criteria

The evaluation of above mentioned inclusion/exclusion criteria will be done at different stages of the study as mentioned below.

4.4.1 Screening Day Activities

The screening will be done within 28 days prior to the dosing of Period-I. After obtaining written Informed Consent, the subjects will be identified via thumb/finger print using computerized software. Following activities will be performed on the day of screening.

a) [redacted]

b) Demography

[redacted]

c) Complete Physical Examination of subjects

Subject's past and present medical / clinical history, vital signs measurement (body temperature, respiratory rate, pulse rate and blood pressure) and systemic examination will be done.

d) 12-Lead Electrocardiogram

A 12-lead ECG will be done.

e) Radiological Examination

Chest X-ray (P/A view) will be done during screening as per the discretion of the principal investigator/co-investigator /Sub-investigator /medical officer if required based on any significant past medical history and/or positive finding in respiratory system examination.

f) Blood and urine laboratory tests

The blood samples will be obtained for haematology, biochemistry and serology screening (HIV, Hepatitis B and C). Pre-study routine urinalysis will also be done. The details of these laboratory tests are given in *Appendix B*.

Subjects qualifying the acceptance criteria for all above examinations and tests will be called on check-in day for Period-I.

[redacted]

Note: Due to ongoing COVID-19 pandemic, the subjects will undergo pre-screening activities in accordance with the SOP titled "Handling of pre-screening activities during COVID-19 pandemic." The subjects will also sign the IEC approved additional subject information sheet and informed consent form for undergoing pre-screening activities and follow general safety instructions during COVID-19 pandemic.

4.4.2 Check-in day activities (Period-I)

Subjects will be identified by thumb/finger print. Thereafter, they will undergo various activities like breath alcohol test, relevant medical /clinical history, physical examination, vital sign measurement (body temperature, respiratory rate, pulse rate and BP) and urine drug abuse test.

[redacted]

[redacted]

4.4.3 Check-in day activities for subsequent period(s)

[redacted].

In addition to the above tests, female subjects will be tested for pregnancy by Serum (β) Beta- hCG (Human Chorionic Gonadotropin) test.

4.5 Subject Withdrawal/ Dropout

Any subject that is discontinued from the study by Medical officer/Principal Investigator for other than personal reasons will be considered as withdrawn.

Subjects may be discontinued from the study for any of the following reasons:

1. Subjects not wishing to continue with the study, irrespective of the reason (dropout subjects).
2. Any significant medical occurrence (including laboratory results) which as per the discretion of the Principal Investigator could be a risk to the health of the subject.
3. Any illness requiring unacceptable medication during the study as per discretion of Principal Investigator.
4. [redacted]

Subject will not be evaluated for the post-study assessment, if he/she is discontinued from the study before dosing in Period-I. Subject may be discontinued from the study for any reason beneficial to his/her well-being.

The Principal Investigator, as well as the sponsor, will decide to withdraw any subject's participation in the study if, in their judgment, continuation in the study may prove harmful to the subject. Such a decision may be precipitated by adverse events, including changes in vital signs, physical examination and 12 lead ECG etc. The Principal Investigator may also withdraw a subject due to poor compliance to the study protocol.

An attempt will be made by the Principal Investigator to find out reason for drop out.

If a subject discontinues from the study any time after being assigned a subject number, the reason will be recorded in the case report form ('withdrawn/dropped out'), by the Principal Investigator/Authorized trained person/Medical Officer. The details of withdrawn /dropped out subjects will be reported in the clinical report.

If a subject discontinues from the study any time after being assigned a subject number before dosing of period I, then principal investigator can replace the dropped out subject with another eligible subject.

5.0 TREATMENT OF SUBJECTS

5.1 Dose Administration

Single oral dose of Investigational medicinal product either of test product (T) or reference product (R1), (R2) and (R3) in sitting position in each period, after an overnight fast of at least 10.00 hrs as per the randomization schedule.

[redacted]

5.2 Medication

If drug therapy other than that specified in the protocol is urgently required during the study or in the washout period, decisions to continue or discontinue the subject will be taken by the PI, based on the following:

- Safety and well-being of the subject.
- Pharmacology and PKs of the non-study medication.

- Likelihood of a drug interaction, which may affect the PK comparison of the study medications.
- The time of administration of the non-study medication, and likelihood of interference in the bio-analysis.

5.3 Monitoring for subject compliance

The subjects will be monitored for compliance to the following restrictions throughout the study period.

5.3.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

6.0 ASSESSMENT OF EFFICACY

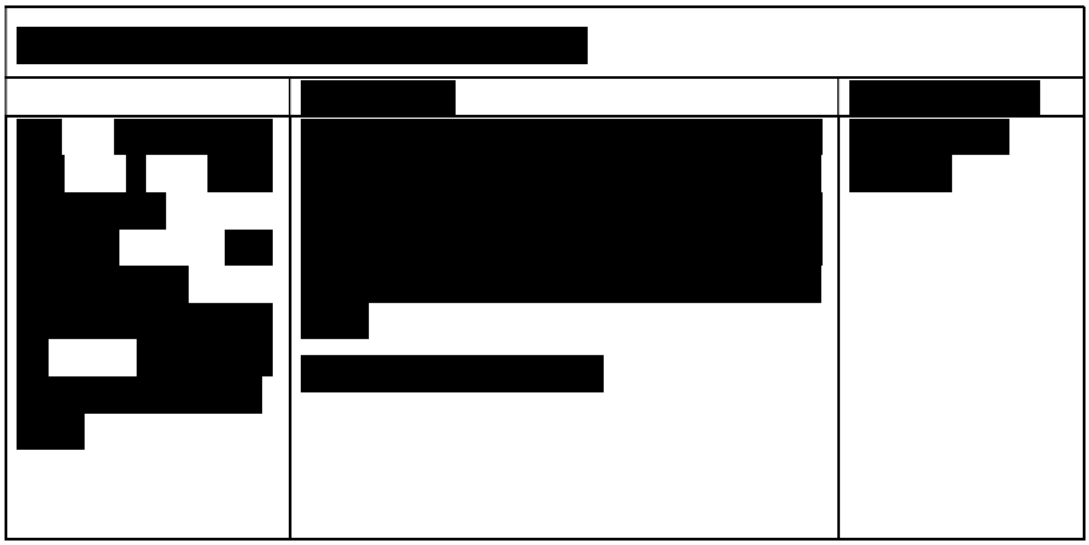
As this is a Pharmacokinetic study, no efficacy measurement will be done. Blood sample collection, handling, processing, bio-analysis and statistical analysis will be done to determine the pharmacokinetic profile of Fixed Drug Combination (FDC) Nefopam Hydrochloride (30 mg) / Paracetamol (500 mg) Tablets.

6.1 Blood Sample Collection

An intravenous cannula will be inserted into the subject's arm for the collection of the blood samples before the pre-dose blood sample and up to 24.00hrs post-dose. If difficulties occur in blood withdrawing or if the subject is not feeling comfortable with the cannula, then the cannula will be removed before 24.00 hrs post-dose and the remaining blood samples will be collected through fresh vein puncture or by recannulation. When meals, vitals and sample collections coincide, samples will be collected first followed by vitals and then meal will be served.

[redacted]

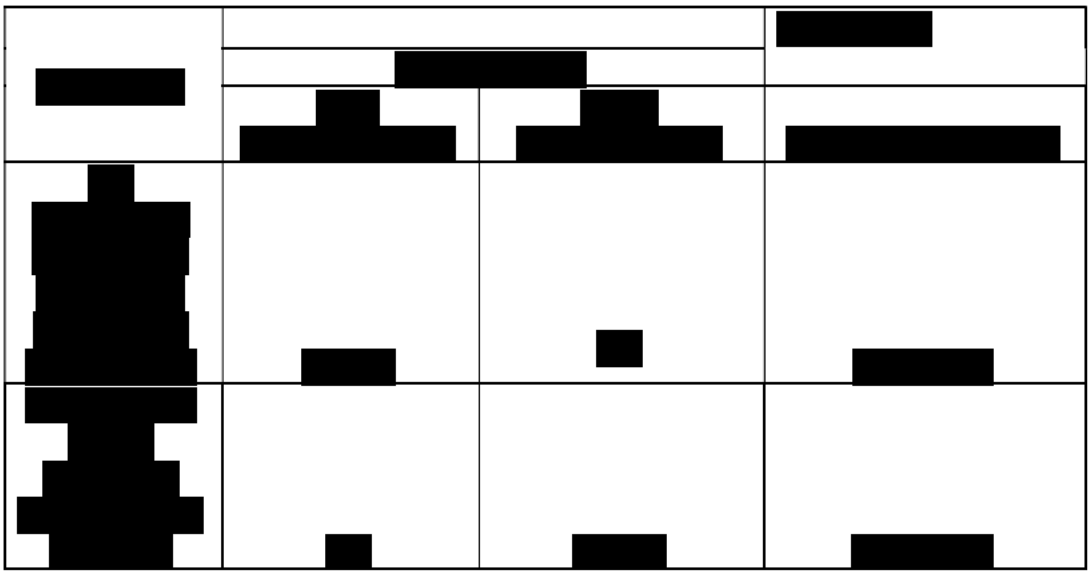
[redacted]



[redacted]

6.2 Sample Handling & Processing

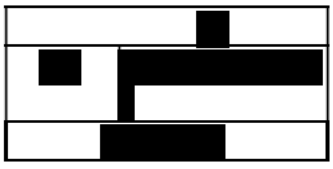
Centrifugation of the samples will be done within 60 minutes after the first blood sample collection of respective time point. [redacted]

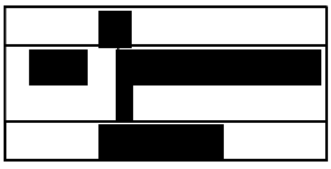


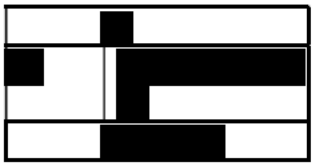
[redacted]

The specimens of label are mentioned below. The number in the first row corresponds to the subject number. Analytical sample for Paracetamol and analytical sample for Nefopam and its metabolite (N-desmethyl-nefopam). Control sample for Paracetamol and Nefopam and its metabolite (N-desmethyl-nefopam). The box next to it denotes 'study code'. [redacted]

[redacted]







[redacted]

with the current version of the SOP for 'Blood sample collection, Processing and Storage'.

Transport of plasma samples from the sample storage area to analytical site will be done as per the current SOP of 'Segregation, Transfer, Retention and Disposal of Biological Samples' and 'Transport of biological samples outside the study centre' maintaining the appropriate storage condition during transportation.

6.3 Bioanalytical Procedure

A validated LC-MS/MS analytical methodology will be used for the determination of Nefopam, Paracetamol and it main metabolites (Sulfate and Glucuronide), N-desmethyl-nefopam in plasma and will be quantified using a validated analytical method from the human plasma samples. Validation of the methodology will be carried out in accordance with applicable guidelines and the current version of the SOP for 'Bio-analytical Method Validation' and other relevant SOPs for Bio-analysis.

Based on the plasma concentrations obtained from the analysis and subsequent statistical analysis, primary PK parameters will be used to assess. In addition, secondary PK parameters will be calculated from the analyzed plasma concentrations.

The batch acceptance or rejection, repetition or reanalysis, if any, will be performed as per predefined criteria laid down in the relevant SOPs for "Batch acceptance of subject sample analysis".

[redacted]

[redacted]

7.0 ASSESSMENT OF SAFETY

The PI will monitor safety data throughout the course of the study. A qualified medical officer will be available during the housing in the clinical center. Subjects will be monitored throughout the study period for occurrence of AEs. A nearby contracted hospital capable of handling emergency situations will be informed about the study. The hospital has agreed to provide the necessary treatment facilities, if required, and the physicians attached to the hospital will carry out treatment of AEs as appropriate, either at the study center or at contracted hospital. Subjects experiencing AEs will be followed up until resolution of the AE. Subjects who at least received one dose of the study medication will be included in the safety analysis.

All data from pre-study and post-study medical and clinical laboratory examinations acquired after signing of the ICF will be documented. Any clinical laboratory result outside the normal range will be evaluated by the PI against the clinical co-relation and study medication if given. The PI will determine whether the laboratory test will be repeated to establish if and when this value returns to normal. Assessments and comments on the clinical significance of laboratory values outside the normal range will be provided by the PI in the clinical report.

The PI should ensure that adequate medical care is provided to a subject for any AE, including clinically significant laboratory values related to the study. The PI should inform a subject when medical care is needed for inter current illness(es) of which the PI becomes aware.

[redacted]

7.1 Safety Evaluation

The subjects will be monitored for occurrence of adverse events and serious adverse events throughout the study. Safety evaluation will be done on the basis of outcomes of physical examination, vital signs measurement and clinical laboratory results. The activities will be performed during each study period and during post study evaluation as given below:

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Additionally, any other assessment including laboratory test(s) will be done if judged necessary by the Principal Investigator (PI) or authorized trained personnel at any time during the course of study.

[redacted]

[redacted]

The reason for not completing the study will be specified in the respective CRF and the clinical report.

The subjects may also report spontaneously any inconvenience or AEs to the monitoring staff at any time during the study or after check-out within the total number of days not exceeding the washout period.

7.2 Handling and Reporting of Adverse Events

Subjects will be monitored throughout the study period for adverse events. Subjects will be specifically asked about any adverse events during the recording of vital signs and will be instructed to bring to the notice of any study personnel of any adverse event that may occur during their stay at the clinical facility.

A medically qualified designate will be available round-the-clock during the period of housing at the clinical facility. Any subject who develops an adverse event will be evaluated by the investigator, will be treated and / followed up until resolution as judged by the investigator.

All AEs including both observed and volunteered ones will be recorded on the appropriate forms, irrespective of its association with the investigational products. The Ethics Committee (EC), Regulatory agency (ies) and the sponsor will be informed regarding the AE as necessary.

7.2.1 Definitions

Adverse Event (or Adverse Experience): Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event (AE) can therefore be 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.

Abnormal laboratory values will be reported as adverse events under the following circumstances:

i. When the abnormal lab report is accompanied with associated symptoms.
ii. When medical/surgical intervention is required

iii. When an additional diagnostic test is required
iv. Leads to serious adverse event
v. When it is considered by Principal investigator as an adverse event

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

Unexpected Adverse Drug Reaction
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product).

Serious Adverse Events (SAE)
"serious adverse event" means an untoward medical occurrence during clinical trial resulting in death or permanent disability, or hospitalization of the trial subject where the trial subject is an outdoor patient or a healthy person, prolongation of hospitalization where the trail subject is an indoor-patient or significant disability or incapacity, congenital anomaly, birth defect or life threatening event.

7.2.2 Severity assessment

The severity of the adverse events will be graded as follows:

- **Mild Adverse Event** – Event results in mild or transient discomfort, not requiring intervention or treatment; does not limit or interfere with daily activities (e.g., insomnia, mild headache).
- **Moderate Adverse Event** – Event is sufficiently discomforting so as to limit or interfere with daily activities; may require interventional treatment (e.g., fever requiring antipyretic medication).
- **Severe and undesirable Adverse Event** – Event results in significant symptoms that prevents normal daily activities; may require hospitalization or invasive intervention (e.g., anemia resulting in blood transfusion).

7.2.3 Causality assessment [5]

Relationship to Investigational Product:
Every effort will be made to obtain all the required information to determine whether the Adverse Event is related to the study procedure or investigational product (causal relationship). In terms of relationship,

Causality term	Assessment criteria
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognized pharmacological phenomenon) • Rechallenge satisfactory, if necessary
Probable /Likely	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Rechallenge not required
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
Unlikely#	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
Conditional /Unclassified	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
Unassessable/ Unclassifiable	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

#Unlikely will be considered as Not Related.
Certain, Probable/ Likely and Possible will be considered as Related.

7.3 Reporting of AEs and SAEs including death

Reporting of AEs

Adverse events will be recorded in adverse event form or appropriate documents. In particular, the information will include description of the event, details of the timing of the event to administration of the study medication, frequency of adverse event, description of the severity of the event, any treatment or diagnostic steps taken in relation to the event, description of the outcome of the event, judgementby the medical officer of any relationship of the event to study medication or procedures. All adverse events will be reported to the sponsor and IEC within 14 calendar days by investigator(s).

Each AE will be evaluated for duration, severity and action taken, outcome and association with the study medication. The study may be suspended or terminated depending upon the seriousness of the AEs.

In the event of unexplained abnormal laboratory test values, the tests should be repeated immediately and followed up as per physician's discretion. Clinically significant laboratory test value abnormalities should be reported as adverse event.

Reporting of SAEs [4]

(1) The investigator shall report all serious adverse events to the Central Licensing Authority, the sponsor or its representative, who has obtained permission from the Central Licensing Authority for conduct of clinical trial or bioavailability or bioequivalence study, as the case may be, and the Ethics Committee that accorded approval to the study protocol, within twenty-four hours of their occurrence; and if the investigator fails to report any serious adverse event within the stipulated period, he shall have to furnish the reasons for delay to the satisfaction of the Central Licensing Authority along with the report of the serious adverse event.

(2) A case of serious adverse event of death shall be examined in the following manner, namely: -

(i) the Central Licensing Authority shall constitute an independent expert committee to examine the cases and make its recommendations to the said authority for arriving at the cause of death and quantum of compensation in case of clinical trial related death;

(ii) the sponsor or its representative and the investigator shall forward their reports on serious adverse event of death after due analysis to the Central Licensing Authority and the head of the institution where the clinical trial or bioavailability or bioequivalence study has been conducted within fourteen days of the knowledge of occurrence of serious adverse event of death;

(iii) the Ethics Committee for clinical trial shall forward its report on serious adverse event of death after due analysis along with its opinion on the financial compensation, if any, determined in accordance with the formula specified in the Seventh Schedule of New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), to be paid by the said sponsor or its representative, who has obtained permission from the Central Licensing Authority for conduct of clinical trial or bioavailability or bioequivalence study, as the case may be, to the Central Licensing Authority within a period of thirty days of receiving the report of the serious adverse event of death from the investigator;

(iv) the Central Licensing Authority shall forward the report of the investigator, sponsor or its representative and the Ethics Committee to the Chairperson of the expert committee;

(v) the expert committee shall examine the report of serious adverse event of death and make its recommendations available to the Central Licensing Authority for the purpose of arriving at the cause of the serious adverse event of death within sixty days from the receipt of the report of the serious adverse event, and the expert committee while examining the event, may take into consideration, the reports of the investigator, sponsor or its representative and the Ethics Committee for clinical trial;

(vi) in case of clinical trial or the bioavailability or bioequivalence study related death, the expert committee shall also recommend the quantum of compensation, determined in accordance with the formula specified in the Seventh Schedule of New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), to be paid by the sponsor

or his representative who has obtained the permission to conduct the clinical trial or the bioavailability or bioequivalence study, as the case may be;

(vii) the Central Licensing Authority shall consider the recommendations of the expert committee and shall determine the cause of death with regards to the relatedness of the death to the clinical trial or the bioavailability or bioequivalence study, as the case may be;

(viii) in case of clinical trial or the bioavailability or bioequivalence study related death, the Central Licensing Authority shall, after considering the recommendations of the expert committee, by order, decide the quantum of compensation, determined as per the formula specified in the Seventh Schedule of New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), to be paid by the sponsor or its representative and shall pass orders as deemed necessary within ninety days of the receipt of the report of the serious adverse event;

(ix) the sponsor or its representative shall pay the compensation in case the serious adverse event of death is related to clinical trial or the bioavailability or bioequivalence study, as specified in the order referred to in clause (viii) of New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) of the Central Licensing Authority within thirty days of the receipt of such order.

(3) Cases of serious adverse events of permanent disability or any other injury other than deaths shall be examined in the following manner, namely:

(i) the sponsor or its representative, and the Investigator shall forward their reports on serious adverse event, after due analysis, to the Central Licensing Authority, chairperson of the Ethics Committee for clinical trial and head of the institution where the trial or bioavailability or bioequivalence study has been conducted within fourteen days of the reporting of serious adverse event;

(ii) the Ethics Committee for clinical trial shall forward its report on serious adverse event of permanent disability or any other injury other than deaths, as the case may be, after due analysis along with its opinion on the financial compensation, if any, determined in accordance with the formula specified in the Seventh Schedule of New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), to be paid by the sponsor or its representative who has obtained permission to conduct clinical trial or the bioavailability or bioequivalence study, as the case may be, within thirty days of receiving the report of the serious adverse event;

(iii) the Central Licensing Authority shall determine the cause of the injury and pass order as specified in clause (iv) of New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), or may constitute an independent expert committee, wherever it considers necessary, to examine such serious adverse events of injury, and such independent expert committee shall recommend to the Central Licensing Authority for the purpose to arrive at the cause of the serious adverse event and also the quantum of compensation, as determined in accordance with formula as specified in the Seventh Schedule of New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) in case of clinical trial or bioavailability or bioequivalence study related injury, within a period of sixty days of receipt of the report of the serious adverse event;

(iv) in case of clinical trial or the bioavailability or bioequivalence study related injury, the Central Licensing Authority shall, by order, decide the quantum of

compensation, determined in accordance with the formula specified in the Seventh Schedule of New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E), to be paid by the sponsor or his representative who has obtained the permission to conduct the clinical trial or the bioavailability or bioequivalence study, as the case may be, within a period of ninety days of receipt of the report of the serious adverse event;

(v) the sponsor or its representative, who has obtained permission to conduct the clinical trial or bioavailability or bioequivalence study, as the case may be, shall pay the compensation in case of clinical trial or bioavailability or bioequivalence study related injury, as specified in the order of the Central Licensing Authority referred to in clause (iv) of New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) within thirty days of receipt of such order.

7.4 Additional Information

- Subjects will be confined in a climate controlled environmental condition from their check-in till discharge from the study facility for each study period.
- All activities related to handling of investigational medicinal products, dosing, blood sample collection, sample handling, processing and sample analysis will be carried out under sodium vapour light.

8.0 STATISTICAL PLAN

Pharmacokinetic and Statistical analysis will be done using SAS® 9.4 version.

The drug concentration of Nefopam, Paracetamol and its main metabolites and N-desmethyl-nefopam in plasma for each subject, each sampling time and each product will be reported.

All concentration values below the limit of quantification (BLQ) will be set to zero for the estimation of pharmacokinetic parameters.

Data from subjects who complete all periods of study will be considered for pharmacokinetic calculations and statistical analysis. Drop-out and withdrawal of subjects should be fully documented. If available, concentration data and pharmacokinetic parameters from such subjects should be presented in the individual listings, but should not be included in the summary statistics.

If the pre-dose value is >5 percent of Cmax, the subject will be dropped from all PK evaluations. The subject data will be reported and included in safety evaluations but shall be excluded from 90% CI calculation.

[redacted]

8.1 Pharmacokinetic Parameters

The following parameters will be calculated for each subject-formulation combination using the non-compartmental model by using statistical package SAS® 9.4 or higher version:

Primary parameters

C_{max}	Maximum observed drug concentration during the study.
AUC_{0-t}	Area under the plasma concentration - time curve measured to the last quantifiable concentration, using the linear trapezoidal rule.

Secondary parameters

AUC_{0-inf}	AUC_{0-t} plus additional area extrapolated to infinity, calculated using the formula $AUC_{0-t} + C_t/K_{el}$, where C_t is the last measurable drug concentration and K_{el} is the elimination rate constant.
T_{max}	Time to observe maximum drug concentration. If the maximum value occurs at more than 1 time point, T_{max} is defined as the first time point with this value.
AUC_{0-t}/AUC_{0-inf}	Ratio of AUC_{0-t} and AUC_{0-inf}
Residual area	Extrapolated area (AUC_{0-inf} - AUC_{0-t})/ AUC_{0-inf}
K_{el}	Apparent first – order terminal elimination rate constant calculated from a semi-log plot of the plasma concentration versus time curve, using the method of least square regression.
$t_{1/2}$	Terminal half-life as determined by quotient $0.693/K_{el}$

[redacted]

8.2 Statistical Method

The calculation of pharmacokinetic parameters and statistical analysis will be performed using the statistical package SAS ® 9.4 or higher version.

[redacted]

The antilog (or exponential) of the limits obtained from the log-transformed data will give the 90% confidence interval for the ratio of geometric means of test and reference formulations.

All the pharmacokinetic parameters will be reported for each subject-product combination and descriptive statistics (mean, standard deviation, coefficient of variation, median, minimum and maximum) will be computed for each pharmacokinetic parameter for each product.

In graphical presentation individual and mean plasma concentration versus time curves will be presented for both untransformed and ln-transformed data.

8.3 Subject Population [8, 9]

[redacted]

8.4 [redacted]

[redacted]

[redacted]

[redacted]

8.4.2 Confidence Interval

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

For Drug-drug interactions [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

For Profiling only:

[redacted]

[redacted]

[redacted]

8.5 Accountability Procedure

8.5.1 Treatment of Missing Values

Missing sample values (MSV) or non-reportable values (NRV), of the plasma concentration data, will be represented as MSV and NRV in the plasma concentration tables and reasons for their missing will be documented. Any BLQ value occurring between two measurable concentration values will also be treated as missing sample (MS). These missing values will be treated as 'missing values' for Pharmacokinetic and statistical analysis. All the procedures will be performed in accordance with current version of SOP for 'Calculation of Pharmacokinetic Parameters'.

[redacted]

8.5.2 Missing samples

Missing samples can be due to withdrawal of subject and accidental spillage of samples as mentioned in current version of SOP for 'Missing Sample'.

8.5.3 Treatment of outliers

Outliers in a data set are defined as observations that appear to be inconsistent with the rest of the data. They can be identified as the values, which completely distort descriptive statistics. Subjects who exhibit extremely high or low bioavailability relative to the reference or test formulation for all log transformed pharmacokinetic parameters is to be based are detected by employing Lund's method (using statistical package SAS® 9.4 or higher version).

A valid clinical or physiological reason will be explored by the Principal Investigator of the study for such an outlier. In case no clinical or physiological reason/justification is identified, the outlier subject will be considered as a valid part of the overall data set and hence the statistical analysis will be performed including outlier subject.

In case clinical or physiological reason/justification is identified, the statistical analysis will be performed excluding the outlier subject to conclude study results. However, to avoid the biasness in the results, the statistical analysis will be performed on both the data sets i.e. including as well as excluding the outliers.

8.6 Treatment of Time Point Deviation

Time deviation for any subject at any time point will be taken care, while calculation of pharmacokinetic parameters.

9.0 DIRECT ACCESS TO SOURCE DATA/DOCUMENTATION

A monitor will visit sometime the study facilities in order to maintain current knowledge of the study through review of the records, comparison with source documents, observation and discussion of the conduct and the progress of the study. The Investigator(s)/institution(s) provide direct access to source data/documents for study related procedures, audits, EC review, and regulatory inspection. Prior to the start of the study, the Principal Investigator/authorized trained person will be contacted and informed of any impending visits and the frequency of such visits. At each visit the Principal Investigator will assist the study monitor in terms of reviewing and verifying those records associated with the study.

10.0 QUALITY CONTROL AND QUALITY ASSURANCE

The Quality Control and Quality Assurance department will confirm that the study is conducted in adherence to the protocol and SOPs for each activity and bioanalysis is performed according to the principles of Good Laboratory Practice (GLP).

In process quality checks and review procedures carried out by The Quality Control and Quality Assurance department will ensure that the activities and the documentation of the data for clinical, bioanalytical and statistical stages are done as per the protocol and / or respective SOP, ICH GCP Guidelines, applicable regulatory requirements. Deviation from the protocol or SOP observed during the quality checks/review will be verified.

11.0 ETHICAL CONSIDERATIONS

The ethical considerations are captured as per New Drugs and Clinical Trials Rules 2019 G.S.R. 227(E) in the applicable sections of protocol and informed consent form.

11.1 Risk and Benefits

[redacted]

Risks of paracetamol

Table 1: Undesirable effects of paracetamol

	Very rare	Undetermined Frequency
Blood and lymphatic system disorders	Thrombocytopenia	In patients with glucose-6-phosphate dehydrogenase [G6PD] deficiency: Haemolytic anaemia is not excluded
Immune system disorders	Cutaneous reactions including erythema, urticaria, angioedema and other signs of anaphylaxis, and Stevens-Johnson syndrome.	
Respiratory, thoracic and mediastinal disorders	Bronchospasm in patients sensitive to aspirin or other NSAIDs	
Hepatobiliary disorders	Hepatic dysfunction	
Skin and subcutaneous tissue disorders	Very rare cases of severe skin reactions have been reported.	

In addition, paracetamol is contraindicated in patients suffering from severe liver insufficiency. Paracetamol repeated administration is contraindicated in patients suffering from anaemia, cardiac and pulmonary pathologies.

[redacted]

Risks of nefopam

[redacted]

Table 2: Undesirable effects of nefopam

	Very common	Common	Rare	Undetermined frequency

Psychiatric disorders			Excitability* Irritability* Hallucination Abuse** Drug-dependence**	Confusionnal state
Nervous system disorders	Drowsiness	Dizziness* Light-headedness Paraesthesia Tremor	Convulsions* Confusion Postoperative confusion Insomnia Headache	Coma
Vascular disorders		Tachycardia* Palpitations* Hypotension	Syncope	
Gastrointestinal disorders	Nausea with or without vomiting	Dry mouth* Abdominal pain Diarrhoea		
Renal and urinary disorders		Urinary retention	Decrease renal function Harmless pink discolouration of the urine	
Eye disorders			Blurred vision	
Immune system, skin and subcutaneous tissue disorders	Sweating*	Allergic reactions	Postoperative hypersensitivity (angioedema, anaphylactic shock) Pruritus Erythema Urticaria Faintness	

*Although never reported, other atropine effects than those described are likely to be observed.
**According to the PRAC conclusions, the suggested plausible mechanism is the inhibition of dopamine recapture.

In addition, nefopam is contraindicated in patients with a history of convulsive disorders and should not be given to patients taking mono-amine-oxidase (MAO) inhibitors. Nefopam is also contraindicated in patients with severe hepatic and / or renal failure.

[redacted]

[redacted]

- elderly patients: due to their slow metabolism, they are more sensitive to adverse effects of the central nervous system: a few cases of hallucination and confusion have been reported in this group of patients.

[redacted]

11.2 Ethics committee review and communications

The study will be conducted after obtaining approval from the Ethics Committee (EC). Documents described in *Appendix G* will be submitted to the EC for review and approval.

Modifications, interfering with the subject's health interests and involving changes in the design of the study or its scientific significance require a new approval of the EC. Any modifications will be signed by investigator and sponsor. All such modifications or subsequent amendments to the protocol prior to commencement of the study will be implemented after written approval of the EC and the sponsor. During the course of the study, the Principal Investigator can do minor administrative or technical modifications that do not interfere with the subject's interest. The same will be conveyed to the EC and the sponsor.

The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior EC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted: (a) to the EC for review and approval/favourable opinion, (b) to the sponsor for agreement and, if required, (c) to the regulatory authority(ies).

The EC will be informed about the study dates. All adverse events will be reported to EC within a specified time.

11.3 Informed Consent Process

This study will be conducted in accordance with the principles of the World Medical Association Declaration of Helsinki (*Appendix D*). All subjects participating in the study will receive detailed information about the study, the procedures, the risks and the medication. All subjects will be required to sign ICF in the presence of the Principal Investigator/authorized trained person before participation in the study. The

photocopy of signed ICF will be provided to all subjects. All signed ICF will be retained in the Trial Master File.

11.4 Confidentiality, Ownership of Data and Coding Procedure:

11.4.1 Confidentiality:

The volunteer's/subject's original medical records (like medical history, physical examination, laboratory results or any other information or data generated during this study) will be strictly kept confidential and shall be only made available to the study related authorities/personnel (sponsor of the study, study monitors or auditors, the insurance company in case of any insurance claim, the Ethics Committee and the national and international regulatory authorities) without violating confidentiality information of volunteer/Subject.

The records identifying volunteer/subjects details will be kept confidential and to the extent permitted by the applicable law and/or regulations will not be made publicly available. If the results of the study are published, then volunteer/subject identity will remain confidential.

11.4.2 Ownership of Data and Coding Procedure:

ACCUTEST acknowledges that all Sponsor's raw data, documentation, Protocols, case report forms, source documents, final reports and investigational products pertaining to Study are the exclusive property of Sponsor. The final results and outcome of the study shall be the sole and exclusive property of Sponsor excluding bio-analytical methods developed and validated on biological matrix by Accutest.

[redacted]

12.0 RECORDING AND ARCHIVING OF DATA:

The CRF will be identified based on volunteer registration number, subject number and study code. Data collected on CRFs during the study will be documented in accordance with current version of SOP for "Recording of Data/Reporting of Results and correcting mistake in documents." Information on demographics, medical history and examination, vital signs, inclusion/exclusion criteria assessment, check in check out details, dosing details, intravenous cannula insertion and removal details, PK sample collection details will be recorded directly on the CRF.

Any error in recording will be struck out with a single line; so as to leave the original data legible, and the new data will be inserted legibly alongside. The correction will be dated and signed. The completed CRFs will be checked by the Principal Investigator/Designee for completeness, accuracy and legibility, for conformance to the source documents.

All information on CRFs will be traceable to source documents, archived in Accutest Research Laboratories (I) Pvt. Ltd. The source documents will have information like laboratory data, ECGs, chest X-ray (if done) etc., and also a copy of the signed informed consent which will indicate study code and study title.

Archived documents will include all essential documents which individually and collectively help in evaluation of the study conduct and the quality of data generated in the Trial master file. These documents will be archived after completion or discontinuation of the study for a period specified in the master service agreement. Prior to destruction of study documents, the sponsor will be notified and consent will be obtained in writing.

13.0 INSURANCE, COMPENSATION AND HANDLING OF STUDY RELATED INJURY/DEATH [4]

The subjects will be adequately compensated as per the compensation policy for the [redacted]

The compensation will be paid in accordance with the following principles.

1. In case of any study related injury sponsor or Accutest Research Laboratories (I) Pvt. Ltd, who has obtained permission to conduct the clinical trial or bioavailability or bioequivalence study, will provide free medical management as long as required or till such time it is established that the injury is not related to the study, whichever is earlier.
2. In case there is no permanent injury, the quantum of compensation shall commensurate with the nature of the non-permanent injury, loss of wages and transportation to the trial subject shall be provided financial compensation by the sponsor or Accutest Research Laboratories (I) Pvt. Ltd, who has obtained permission to conduct the clinical trial or bioavailability or bioequivalence study.
3. In case of any study (clinical trial) related death of the subject, Accutest Research Laboratories (I) Pvt. Ltd. or sponsor who has obtained permission to conduct the clinical trial or bioavailability or bioequivalence will provide compensation to subject's nominee.
4. Any injury or death of the subject occurring in study due to following reasons shall be considered as study related injury or death.
   a. adverse effect of investigational product(s);

b. violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator;
c. adverse effects due to concomitant medication excluding standard care, necessitated as part of approved protocol;
d. for injury to a child in–utero because of the participation of parent in study;

[redacted]

14.0 REPORT

Final report containing the clinical, analytical and statistical sections will be prepared as per ICH E3 guideline 'Structure and Content of Clinical Study Reports' unless specified. The Study Report will contain supporting tables for various pharmacokinetic parameters, adverse events and conclusion. [redacted].

15.0 PUBLICATION POLICY

Publication of the results is at the sole discretion of the study sponsor.

16.0 CHANGES IN PROTOCOL

Any change or addition to this protocol after its approval, but prior to the initiation of the study, will require a written protocol amendment, which must be approved by Principal Investigator, sponsor and the EC before implementation. Any deviation from the approved protocol, during the conduct of the study will be documented as a 'Protocol Deviations'.

APPENDIX A (MEALS)

[redacted]

[redacted]

Abbreviation:-CHO: carbohydrates, g: grams, no:number, pc: piece, ml: milliliter

Nutritive Value of the Day's Menu				
Description	**CHO** [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]	[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]
		Tomato, 30g	1.08	0.27	0.06	6
		Green peas, 15g	2.4	1.1	0.0	14
		Cooking oil, 6.5g	0.0	0.0	6.5	58
		Butter, 3g	0.0	0.0	2.4	22
		Lemon, 2pcs	0.2	0.02	0.018	1.14
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
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[redacted]						
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	[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]

		Oil, 5g	0.0	0.0	5.0	45
[redacted]						

Abbreviation:-CHO: carbohydrates, g: grams, no:number, ml: milliliter, pc: piece, NA: not applicable

Nutritive Value of the Day's Menu				
[redacted]				

Please note: Food items mentioned in the menu plan may be altered, subject to availability and within limitations of the'Food Exchange List' being currently followed for 'menu planning' at Accutest Research Laboratories (I) Pvt. Ltd. Alterations are as per the solitary

[redacted]

APPENDIX B

CLINICAL LABORATORY TESTS

[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]		
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
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[redacted]	[redacted]	[redacted]
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[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

APPENDIX B (Contd…)

Clinical Laboratory Tests

Test Description	Reference range	Clinically Acceptable Limit
Infectious Disease Screening		
HIV-1 & HIV-2 Antibodies	Reactive / Non-Reactive	Non-Reactive
Hepatitis B	Reactive / Non-Reactive	Non-Reactive
[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]	0-10 /hpf	0-10 /hpf
Casts	Absent	(+)
Crystals	Absent	(+)
Bacteria	Absent	Absent

APPENDIX B (Contd…)
Clinical Laboratory Tests

Urine Examination For Drug of Abuse	
Test Description	**Reference range**
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]/blood.

If applicable.

Note:

1. If laboratory values are within normal range, it will be classified as Normal (N).
2. If laboratory values are outside normal range, but within acceptable range, it will be classified as Not Clinically Significant (NCS).
3. If any parameter is outside acceptable range without any associated clinical sign/symptom(s), it will be considered as Not Clinically Significant (NCS) at the discretion of medical personnel.

[redacted]

APPENDIX C
SCHEDULE OF STUDY EVENTS

					√	

Note: Additionally, any other assessment including laboratory test(s) will be done if judged necessary by the Principal Investigator (PI) or medical officer at any time during the course of study.

APPENDIX D
(WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI)
Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
59th WMA General Assembly, Seoul, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”
4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are Involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.
5. Medical progress is based on research that ultimately must include studies involving human subjects.
6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.
7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.
8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.
10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.
11. Medical research should be conducted in a manner that minimizes possible harm to the environment.
12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.
13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.
14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.
15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.
17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.
18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.
22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious AEs. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

    After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed. All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such

research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances: Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; orWhere for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention. Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.
36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

APPENDIX E

[redacted]

Compensation Details			
Compensation Head	**INR (`)**	**Multiplier**	**Total Amount (`)**
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
Total			
Rounding off to next figure in multiple of 100			

[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]

APPENDIX F

REFERENCES

1. [redacted]

9. [redacted]

APPENDIX G

LIST OF DOCUMENT SUBMITTED TO EC

1. Stud
2. Info
   lang
3. Liter
4. Upd
5. Inve
6. Any

[redacted]