AN OPEN-LABEL, SINGLE TREATMENT, SINGLE PERIOD, SINGLE BUCCAL DOSE PHARMACOKINETIC STUDY OF PARACETAMOL UNIFLASH (125 MG/ 1.25 ML) IN HEALTHY, ADULT, HUMAN SUBJECTS UNDER FASTING CONDITIONS.

Clinical study protocol: UP-CLI-2021-002

Version: 1.0 – 01 Mar 2022

Sponsor	**UNITHER Pharmaceuticals** 3-5 Rue Saint-Georges 75009 Paris France
Test product	Paracetamol Uniflash (Compound number: 08P1703F0)
Development Phase	Pharmacokinetic Study
EudraCT number	2021-005315-31

CRO

Raptim Research Pvt. Ltd.,

PAP-213, PAP-A-218 and PAP-A-219
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STUDY APPROVAL AND MANAGEMENT TEAM

Study Investigator Approval

I, the undersigned, have read and understood this protocol, and hereby agree to conduct the study in accordance with this protocol, Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, 64th World Medical Association – General Assembly, Fortaleza, Brazil, October 2013)[1], Good Clinical Practice (International Council for Harmonization – E6 (R2) Guidelines, Current Step 4 Version, dated 9 Nov 2016)[2], New Drugs and Clinical trials Rules, 19 March 2019, Ministry of Health and Family Welfare, Government of India[3], CDSCO Guidelines for Bioavailability & Bioequivalence Studies Mar 2005[4], Indian Council of Medical Research (Ethical Guidelines for Biomedical Research on Human Participants, 2017)[5], Guidance on the Investigation of Bioequivalence, CHMP – EMA (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**, Jan 2010), ethical requirements of Directive 2001/20/EC[6] and other applicable regulatory requirements.

I agree to comply with all relevant Standard Operating Procedures required for the conduct of this study and to ensure that all associates participating in the conduct of this study are informed regarding their obligations.

Sponsor'approval

I the undersigned, have read and understood this protocol, and hereby agree to abide by the pertinent responsibilities and obligations of Sponsor for the conduct of the study in accordance with Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, 64th World Medical Association – General Assembly, Fortaleza, Brazil, October 2013)[1], Good Clinical Practice (International Council for Harmonization – E6 (R2) Guidelines, Current Step 4 Version, dated 9 Nov 2016)[2], New Drugs and Clinical trials Rules, 19 March 2019, Ministry of Health and Family Welfare, Government of India[3], CDSCO Guidelines for Bioavailability & Bioequivalence Studies Mar 2005[4], Indian Council of Medical Research (Ethical Guidelines for Biomedical Research on Human Participants, 2017)[5], Guidance on the Investigation of Bioequivalence, CHMP – EMA (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**, Jan 2010), ethical requirements of Directive 2001/20/EC[6] and other applicable regulatory requirements.

I further assure that the investigational medicinal products (test drugs) to be used in this study are manufactured as per the current Good Manufacturing Practices.

[redacted]

Study management Team

Sponsor UNITHER Pharmaceuticals	[redacted] Manager
Contract Research Organization Raptim Research Pvt. Ltd., Navi Mumbai, India.	[redacted]

FACILITIES INVOLVED IN THE STUDY

Screening Facility	[redacted]
Clinical Facility	Raptim Research Pvt. Ltd., [redacted]
Bioanalytical and Statistical Facility	Raptim Research Pvt. Ltd., [redacted]
Bioanalytical Facility (For Gas Chromatography)	[redacted]
Clinical Laboratory	[redacted]

	[redacted]
Emergency Care Unit	Criti-care ICCU, Multispecialty & Trauma Centre, [redacted]
Bio-waste Management Unit	[redacted]
Independent Ethics Committee	[redacted]

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LIST OF ABBREVIATIONS

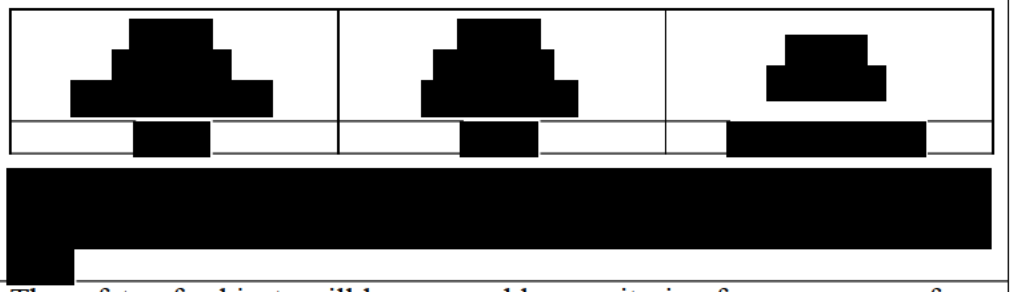
Abbreviation	Full Form
ADL	Activities of Daily Living
AE	Adverse Event
ALP	Alkaline Phosphatase
ANOVA	Analysis of Variance
API	Active Pharmaceutical Ingredient
$AUC_{0\text{-}inf}$	Area under the plasma concentration versus time curve extrapolated to infinity. $AUC_{0\text{-}inf}$ is calculated as a sum of the $AUC_{0\text{-}t}$ and the ratio of last measurable plasma concentration to the elimination rate constant, calculated using the formula $AUC_{0\text{-}t} + C_t/K_{el}$. Where C_t is the last measurable drug concentration and K_{el} is the elimination rate constant.
$AUC_{0\text{-}t}$	Area under the plasma concentration versus time curve, from time 0 to the last measurable concentration time, calculated using the trapezoidal rule.
$AUC_{\%Ratio}$	Percent ratio of $AUC_{0\text{-}t}$ and $AUC_{0\text{-}inf}$
$AUC_{\%Extrapolated}$	Percentage area extrapolated from last measurable time point to infinity, calculated using the formula $\{(AUC_{0\text{-}inf} - AUC_{0\text{-}t}) / AUC_{0\text{-}inf}\}$ X 100
BA	Bioavailability
BE	Bioequivalence
°C	Degree Celsius
CDSCO	Central Drugs Standard Control Organization
CFR	Code of Federal Regulations
CI	Confidence Interval
C_{max}	Maximum measured plasma concentration of drug
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee For Proprietary Medicinal Products
CPU	Clinical Pharmacology Unit
CRF	Case Report Form
CRO	Contract Research Organization
DCGI	Drugs Controller General of India
ECG	Electrocardiogram
EMA	European Medicine Agency
GCP	Good Clinical Practice
HBsAg	Hepatitis B Surface Antigen
hCG	Human Chorionic Gonadotropin

Abbreviation	Full Form
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HPLC	High Pressure Liquid Chromatography
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
ISCV	Intra-subject Coefficient of Variation
K_3EDTA	Tripotassium Ethylene Diamine Tetra Acetic Acid
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 squares regression. The parameter will be calculated by linear least-squares regression analysis in the terminal log-linear phase (using three or more non-zero plasma concentrations)
LC-MS/MS	Liquid Chromatography - Mass Spectrometer/Mass Spectrometer
LSM	Least Squares Mean
Ln	Natural Logarithm
OTC	Over The Counter
PK	Pharmacokinetic
QA	Quality Assurance
QWP	Quality Working Party
RCF	Relative Centrifugation Force
RPM	Revolutions per minute
SAS	Statistical Analysis Software
SAE	Serious Adverse Event
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SIS	Subject Information Sheet
SOP	Standard Operating Procedures
$t_{1/2}$	The apparent first-order terminal half-life will be calculated as $0.693/K_{el}$
T_{max}	Time of the maximum measured plasma concentration. If the maximum value occurs at more than one time point, T_{max} is defined as the first time point with this value.
WBC	White Blood Cell

STUDY SYNOPSIS

Study Title	An open-label, single treatment, single period, single buccal dose pharmacokinetic study of paracetamol Uniflash (125 mg/ 1.25 mL) in healthy, adult, human subjects under fasting conditions.
Study Design	An open label, single treatment, single period, single buccal dose pharmacokinetic study under fasting condition.
Study Objectives	**Primary Objective:** To assess the Pharmacokinetic profile of paracetamol of the Test Product. [redacted]
Study Population	A total of 32 + 02 standby* healthy, adult human subjects will be enrolled in the study. [redacted]
Investigational Medicinal Products(IMPs)	**Test product (A):** Paracetamol Uniflash (125 mg/ 1.25 mL) (Compound Number: 08P1703F0) of UNITHER Pharmaceuticals.
Screening Procedures	Screening procedures will be performed within 21 days prior to check-in of the period and screening will include registration/identification in biometric system, obtaining written screening consent, demographic parameters, medical and medication history, physical examination, vital signs measurements (blood pressure, pulse rate, body temperature and respiratory rate), 12-lead ECG recording, laboratory investigations (hematology, biochemistry, serology and urine analysis), urine pregnancy test, gynecological history (for female subjects) and evaluation of inclusion and exclusion criteria.
Check-in Activities	Prior to check-in, the activities performed will include biometric identification, obtaining study specific written informed consent (only during the first period), urine alcohol test, urine screen for drugs of abuse, serum β-hCG test (for female subjects), physical examination, vital signs measurements (blood pressure, pulse rate, body temperature and respiratory rate), assessing general well-being since last visit and evaluation of inclusion and exclusion criteria.

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted] time will be reported as PK sampling deviations as per in-house SOP.

	Reason for delay will be documented (in CRF) for blood samples collected beyond +2 minutes. Actual sampling time will be taken into consideration for PK calculations.
Total Blood Loss	Total blood loss for a subject during the study will not exceed 111.0 mL (for male subjects) or 113.0 mL (for female subjects).
Blood Sample Processing	[redacted]  [redacted]
Safety Monitoring	The safety of subjects will be assessed by monitoring for occurrence of any Adverse Event (AE) as well as vital signs and general well-being during the in-house stay. [redacted] Physical examination, and vital signs measurements (blood pressure, pulse rate, body temperature, and respiratory rate) and well-being will be evaluated at check-out (-02.00 hours from scheduled time) during the study period, and during the occurrence of any AE or at the time of subject termination/withdrawal from the study. Physical examination and vital signs measurements (blood pressure, pulse rate, body temperature and respiratory rate) will be performed for standby subjects during their check-out. Well-being and cannula site examination will be evaluated after the last in-house blood sample collection in the study period.
Check-out	Subjects will be checked out after 12.00 hours post-dose during the study period.
Post-study Safety Assessments	Post-study safety evaluations will be performed after 12.00 hours post-dose (-02.00 hours from scheduled time, except blood sample collection for post-study safety evaluation) or at the time of subject withdrawal/termination. Post-study safety assessments will include physical examination, vital signs

	measurements (blood pressure, pulse rate, body temperature and respiratory rate), well-being, and blood sample collection for laboratory analysis [hematology, biochemistry (Serum creatinine, SGOT/AST, SGPT/ALT, Serum bilirubin–Total, Serum blood urea nitrogen)]. Note: As check-out of last study period and post-study safety assessments are to be performed at the same time, physical examination, vital signs measurements, well-being and cannula site examination will be performed only once at check-out of last study period.
Bioanalysis	Plasma samples will be analyzed for Paracetamol and Ethanol using a validated method in accordance with EMA guidelines and in-house SOPs of bioanalytical laboratory.
PK Parameters and Their Evaluations	The following PK parameters will be calculated for both paracetamol and ethanol using a non-compartmental model of Phoenix®WinNonlin® - Software, Version 8.3.4 or higher (Certara USA, Inc.): • PK parameters: C_{max}, [redacted] $AUC_{0\text{-inf}}$ [redacted]

1. 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. Paracetamol as part of the therapeutic strategy for pain management

Management of patients with acute pain begins by identifying the underlying cause and using a disease-specific treatment as necessary. Treatment of pain should aim to decrease the intensity of acute pain and to reduce or prevent permanent changes in the nervous system that may result in chronic pain.

The World Health Organization (WHO) created 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.

Paracetamol has analgesic and antipyretic effects and is the only remaining para-aminophenol used in clinical practice. It is the most widely used over-the-counter and prescription analgesic worldwide and is part of the first step of the WHO pain ladder. Paracetamol is recommended as a first-line therapy in several international guidelines for the management of a variety of acute and chronic conditions [12].

The mechanism of action of paracetamol remains unclear. In contrast with opioids, paracetamol has no known endogenous binding sites, and, unlike nonsteroidal anti-inflammatory drugs (NSAID), it does not inhibit peripheral cyclo oxygenase activity. The analgesic efficacy of paracetamol may be due to central antinociceptive effects through direct and indirect inhibition of central cyclo-oxygenases, and also through activation of the endocannabinoid system and spinal serotonergic pathways [13, 14, 15, 16]. In

addition, independent of any cyclo-oxygenase activity, paracetamol down-regulates prostaglandin production at the cellular transcriptional level [17].

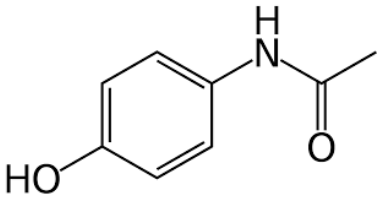
Under normal conditions of use, paracetamol is generally considered to be safer than other commonly used analgesics such as NSAIDs or opioids. The long-term observational evidence of the harmful effects of paracetamol has been summarized in a systematic review of studies investigating the association between paracetamol and major adverse events (AEs) in the general adult population[18]. This review demonstrated a consistent dose-response relationship between paracetamol at standard analgesic doses and AEs that are often observed with NSAIDs. Mortality, cardiovascular, gastrointestinal and renal AEs were all increased with increasing doses of paracetamol.

In order to markedly reduce the risk of drug-induced side effects, paracetamol daily dose intake should be reduced. One possibility of achieving this, is modifying the form of intake as lower doses of paracetamol are required for effective pain relief.

1.3. Rational for paracetamol UNIFLASH

Paracetamol UNIFLASH is a new form of paracetamol dissolved in an ethanol/water solution (50/50), which has been developed for buccal use.

Table 1: Brief introduction of investigational medicinal product

Chemical Name	N-(4-hydroxyphenyl) acetamide, N-(4 hydroxyphenyl) ethanamide
Empirical formula	$C_8H_9NO_2$
Molecular weight	151.163 g/mol
Structural formula	
General description	Paracetamol, also known as acetaminophen, is a medication used to treat fever and mild to moderate pain.

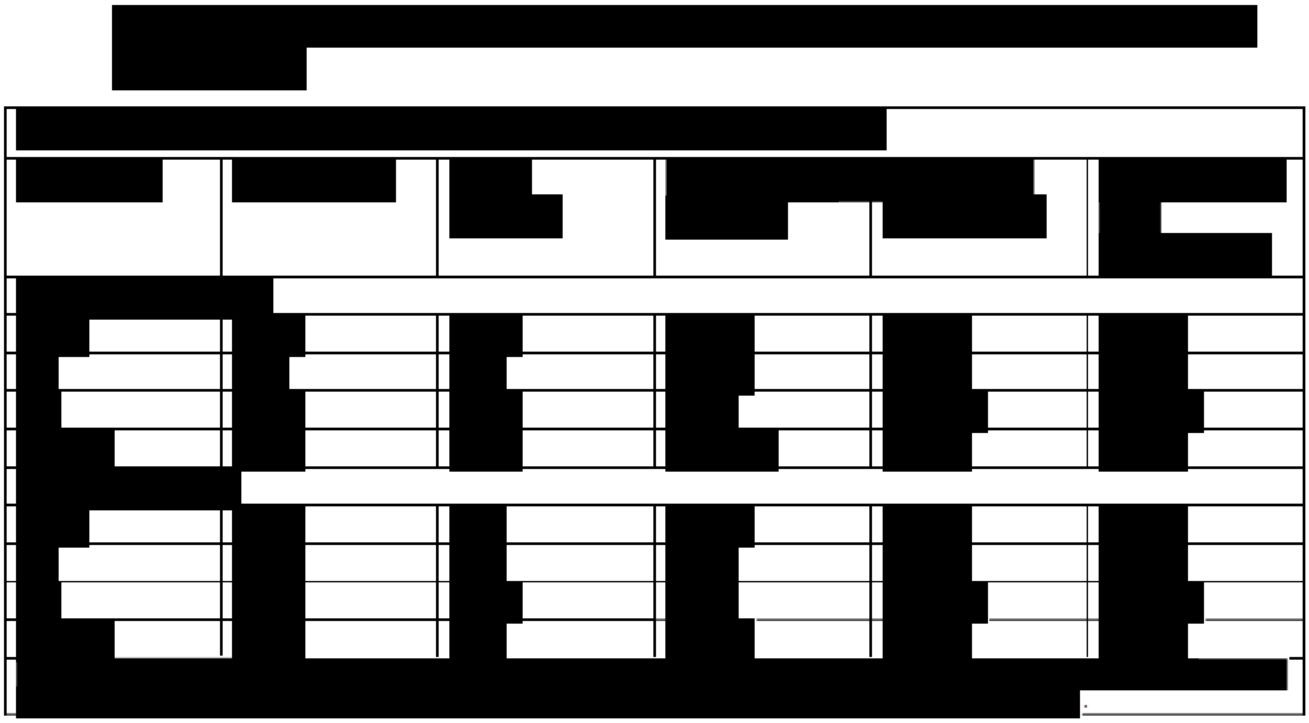
The solvent ethanol is able to pass through oral mucosal tissues by disrupting intercellular lipids [19], and dissolving drugs in this solvent allows them to be transported through oral mucosa [20]. The development of a form of paracetamol dissolved in ethanol and water will enhance drug absorption from the oral mucosa and bypass first pass metabolism by the liver thereby allowing a rapid onset of action.

This development of the paracetamol UNIFLASH formulation aims to significantly reduce the amount of paracetamol administered per dose while maintaining the same level of efficacy as a standard oral dose of paracetamol. In reducing the risk of overdose with paracetamol the new formulation should be able to increase the benefit risk ratio of the treatment.

[redacted]

1.4. Pharmacokinetics

[redacted]



1.5. Indication and usage

Acetaminophen (acetyl-p-aminophenol; APAP; paracetamol) is an effective analgesic for mild and moderate pain and fever

1.6. Potential risk related to Investigational Medicinal Product

Paracetamol UNIFLASH contains paracetamol. As a result, subject treated with Paracetamol UNIFLASH might experience the adverse reactions already reported in the SmPCs for paracetamol oral administration.

1.6.1. Contraindication

Paracetamol UNIFLASH is contraindicated in patients with a known hypersensitivity to paracetamol or any of the other constituents.

Study drug will not be given to subject with severe hepatic or renal impairment.

Repeated administration of Paracetamol is contraindicated in patients with anaemia, heart disease, and pulmonary disease.

1.6.2. Special Warnings and special precautions for use

Special warnings and precautions for use do not differ from those of the paracetamol indicated in the SmPC of Panadol® dated Oct 2019.

Potential risks related to paracetamol:

- use of enzyme inducers, such as barbiturates and anticonvulsants, excessive alcohol consumption,
- hepatic and / or renal impairment,
- chronic consumption of paracetamol may cause kidney failure,
- glutathione depletion – especially in patients with severe malnutrition, low body mass index, anorexics, chronic alcoholics, in case of gluthatione deficiency like in septicaemia case, IMP can increase the risk of metabolic acidosis,
- elderly patients are more sensitive and more at risk of liver or kidney failure.

Taking too much acetaminophen may cause serious (possibly fatal) liver disease. Adults should not take more than 4000 milligrams (4 grams) of acetaminophen a day. People with liver problems and children should take less acetaminophen.

1.6.3. Interaction

Interactions do not differ from those of the paracetamol indicated in the SmPCs of Panadol®.

- administration of activated charcoal decreases the absorption of paracetamol in case of overdose,
- hepatic enzyme inducers (such as barbiturates, diphantoin) and alcohol may increase the hepatotoxicity of paracetamol,
- the half-life of chloramphenicol can be prolonged from 2 to 3 hours to 18-24 hours when concomitant use of paracetamol is used,
- the low binding of paracetamol to plasma proteins allows its association with anticoagulants. However, taking paracetamol for several days may increase the risk of bleeding. In this case, the regular check of the International Normalized Ratio (INR) is recommended,
- due to the risk of decreased leukocyte (leukopenia) levels when concomitant administration of paracetamol and AZT (zidovudine), simultaneous administration will only be with medical advice,
- paracetamol absorption may increase with metoclopramide and decrease with cholestyramine. Concomitant administration of diflunisal increases serum paracetamol levels. High serum paracetamol levels have been associated with hepatotoxicity.

1.6.4. *Adverse reactions*

Adverse reactions expected do not differ from those of the paracetamol.

The tables below are presented according to the MedDRA system organ classification (SOC) and Preferred Term Level.

According to the Belgian SmPC of Panadol® (comparator of the phase III study), the expected frequency of adverse reactions is presented in the tables below in CIOMS frequency categories:

- 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.

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.	-

1.6.5. Overdose, drug abuse and dependence

Recommendations regarding overdose, drug abuse and dependence do not differ from those of the paracetamol and are detailed in the Investigator Brochure. It will not be applicable for this study as only a single dose is given to the patient.

1.6.6. Effects on ability to drive and use machine

Paracetamol has no effect on the ability to drive and use machines.

2. STUDY RATIONALE

Paracetamol is the most widely used analgesic worldwide.

In the context of guidelines recommending lower paracetamol doses per intake in order to markedly decrease the corresponding daily consumption and the risk of drug-induced side effects such as hepatic ones, UNITHER Pharmaceuticals has developed a new paracetamol formulation for buccal use (paracetamol UNIFLASH 125 mg). This route of administration aims to use lower doses of paracetamol thereby improving its corresponding safety profile, especially by avoiding the hepatic first pass effect.

Further to the encouraging results of the initial Proof of Concept (POC) studies, [redacted]

The aim of this bioavailability study UP-CLI-2021-002 is to assess the pharmacokinetic profile of the new formulation of 125 mg/1.25mL paracetamol UNIFLASH oromucosal solution (compound 08P1703F0), [redacted]

3. STUDY OBJECTIVES

Primary Objective: To assess the pharmacokinetic profile of paracetamol of the Test Product.

[redacted]

4. INVESTIGATIONAL PLAN

4.1. Study design

An open label, single treatment, single period, single buccal dose pharmacokinetic study under fasting condition.

4.2. Selection and handling of study population

A total of 32 + 02 standby* healthy, adult human subjects will be enrolled in the study.

*Standby subjects, will be enrolled in the study as standby and available until dosing of the period. The standby subjects will replace discontinued subjects (if any) before dosing

to ensure dosing of 32 subjects. All the protocol procedures and restrictions will be followed for these standby subjects until dosing.

If the standby subjects are replaced, then these subjects will be numbered as 33, 34.

4.2.1. Inclusion criteria

A subject fulfilling the following criteria will be included in the present study:

- Willing to provide written informed consent for participation in the study, and an ability to comprehend the nature and purpose of the study;
- Willing to be available for the entire study period and to comply protocol requirements;
- Healthy, adult, human subject of 18-45 years (both inclusive) of age;
- Body mass index in the range of 18.50 – 30.00 kg/m^2 (both inclusive);
- Normal health status as determined by baseline medical and medication history, at the time of screening and vital signs measurements and physical examination at the time of screening as well as check-in of the study period;
- [redacted]

4.2.2. Exclusion criteria

A subject with the following criteria will be excluded from the study:

- Any medical or surgical conditions, which might significantly interfere with the functioning of gastrointestinal tract and of blood forming organs;
- Significant history or current evidence of malignancy or chronic - infectious, cardiovascular, renal, hepatic, ophthalmic, pulmonary, neurological, metabolic (endocrine), hematological, gastrointestinal, dermatological, immunological or psychiatric diseases, or organ dysfunction;
- [redacted]

4.2.3. Discontinuation criteria

Subject will be considered as discontinued based on the following criteria:

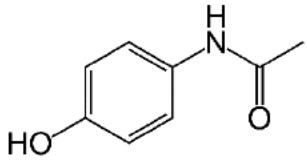
- Withdrawal: Subject's decision to withdraw his/her voluntary participation, anytime during the study period.
- Termination: The clinical investigator may terminate a subject from the study for any of the valid reasons, which is appropriate in view of the safety and well-being of subject, GCP principles or objectives of the study, in particular for but not limited to:
  - ✓ Any serious adverse event (SAE) during the study;

[redacted] safety assessments will be performed as per procedures mentioned in section 9.8.8.

4.3. Identity of Investigational Medicinal Products

The description of study investigational medicinal products (IMPs) is represented in table 2 below.

[redacted]

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

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

4.4. Randomization

Not Applicable. As this is single period study all subjects will receive Test Product (A).

4.5. Blinding

The study has been designed as an open label and all the study staff as well as the subjects will be unblinded to the treatment assigned in the study period.

4.6. Packaging, labelling and shipment

[redacted]

4.6.1. Packaging

[redacted]

[redacted]

4.6.2. *Labelling*

The content of the labelling will be in accordance with the local regulatory specifications and requirements.

[redacted]

[redacted]

- [redacted]
- [redacted]

- [redacted]

[redacted]

4.6.3. Shipment of IMP

Shipments of IMP to site will be organized by the Sponsor's drug distributor [redacted]

[redacted]

[redacted]

4.7. Handling of Investigational Medicinal product

4.7.1. Receipt

The investigational medicinal product(s) shipment will be received by the clinical investigator or his/her designated personnel or pharmacist.

After receipt of the IMPs, identification of the IMPs will be done as per in-house SOP and acknowledgment along with discrepancies (if any) will be informed to the sponsor.

4.7.2. *Storage conditions*

In accordance with local regulations, labelling specifications, policies, and procedures, [redacted]

4.7.3. *Dispensing*

The pharmacist will be responsible for the dispensing of the required number of test product [redacted]

4.7.4. *Method of IMP Administration*

[redacted]

4.7.5. *Accountability and retentions of Investigational medicinal product*

[redacted]

[redacted]

4.8. Clinical operation procedures

4.8.1. Screening activities

The following activities will be performed within 21 days prior to check-in to screen the subjects:

- [redacted]

Table 3: Laboratory Investigations

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

*At the time of check-in of the study period.
#At screening only

These medical and laboratory investigations with values out of acceptance range will be individually evaluated for their clinical significance. Subjects will be eligible for enrolment in the study only if these values are deemed clinically non-significant.

4.8.2. Check-in activities and housing period

[redacted]

4.8.3. Restrictions

4.8.3.1. *Diet*

[redacted]

4.8.3.2. Posture

[redacted]

[redacted]

[redacted]

4.8.4. Dosing and its compliance assessment

[redacted]

[redacted]

[redacted]

[redacted]

4.8.5. Concomitant medication

The restrictions regarding any medication or OTC products or herbal products will be followed as per the exclusion and restriction criteria. If a drug other than that specified in the protocol is required to be administered to the subject during study or washout period, decisions to continue or discontinue the subject will be taken by the Clinical Investigator and will be based on the following:

- Safety and well-being of subject
- Pharmacodynamic and PK interaction
- The time of administration of the non-study medication, and likelihood of interference in bioanalysis.

Subject must inform the Clinical Investigator/Clinical Co-Investigator regarding any medication consumed during course of the study. Medications received other than the investigational medicinal product will be documented in the case report forms. The details of all the concomitant medications used in the study will be provided to the bioanalytical team before bioanalysis.

4.8.6. Blood sampling procedures and processing

4.8.6.1. Cannulation

[redacted]

4.8.6.2. Sampling schedule and collection

[redacted]

4.8.6.3. *Sample processing and transfer*

Blood samples will be centrifuged at 4000 RPM for 10 minutes at 5°C ± 3°C to separate the plasma. The plasma samples will then be separated as mentioned in below table into pre-labeled polypropylene tubes, and will be stored in the deep freezer maintained at -20°C (-15°C to -25°C) within 60 minutes of blood sample collection of each time point.

Plasma Aliquot 01 (for Paracetamol)	Plasma Aliquot 02 (for Ethanol)	Plasma Aliquot 03
0.6 mL	1.0 mL	Rest of the plasma

[redacted]

[redacted]

[redacted]

4.8.7. Safety monitoring

During the study period, safety of a subject will be monitored by:

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

- [redacted]

[redacted]

4.8.8. *Post-study safety evaluations*

[redacted]

[redacted]

4.8.9. *Check-out*

Subjects will be checked out after 12.00 hours post-dose during the study period.

4.8.10. *Total blood loss*

[redacted]

[redacted]

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

[redacted]

5. SAFETY CONSIDERATIONS

5.1. Risk and benefits to study subjects

Participation in BE/BA studies yields no direct benefit (medical benefit) to the subjects. The subject may experience AEs due to investigational medicinal product or due to study related procedures. The risks as described above are low considering the fact that only single low dose will be administered.

5.2. Definitions related to safety

5.2.1. Adverse event

An AE (or adverse experience) is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. It can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Also, abnormal results of diagnostic procedures are considered to be AE, if the abnormality results in subject withdrawal, is associated with SAE, leads to additional treatment or to further diagnostic tests or is considered to be of clinical significance by the clinical investigator / clinical co-investigator.

5.2.2. Adverse drug reaction

In the pre-approval clinical experience with a new medicinal product or its new usages, [particularly as the therapeutic dose(s) may not be established], all noxious and unintended responses to a medicinal product related to any dose will be considered adverse drug reactions. The phrase "responses to medicinal products" means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed medicinal products, an adverse drug reaction in the post-marketing setting is a response to a drug which is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

5.2.3. Unexpected adverse drug reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed.

5.2.4. Serious adverse event or adverse drug reaction

A SAE is any untoward medical occurrence that at any dose:

- results in death;
- permanent disability;
- is life-threatening [The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe;
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity, or;
- is a congenital anomaly/birth defect.

Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These will also usually be considered serious.

5.3. Adverse event documentation and reporting

All AE complaints, signs or symptoms that are reported will be recorded in the AE Form as part of CRF. In particular the information will include details of administration of the investigational medicinal product and details of AE with its date and onset time, causality, frequency, severity, outcome, and if any treatment or diagnostic steps taken in relation to it. All AEs will be followed until resolution, except in case of lost to follow up. This may involve additional visits of the subject to the clinical facility.

All the AEs will be evaluated on the basis of severity, causality and outcome as given in the below table.

Table 6: AE Evaluation Based on Severity, Causality and Outcome

Parameter	Description
Severity	
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.
Causality	
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.
Outcome	
Resolved / Resolved with sequel / Ongoing / Lost to follow-up/ Stable chronic condition / Continuing at death / Death	

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

Pre-existing medical conditions or symptoms occurring prior to the initiation of the study will not be reported as AEs. A worsening of a pre-existing medical condition or

symptom will be reported as an AE. Any AE regardless casualty relationship will be recorded and reported to the Independent Ethics Committee (IEC).

AEs will be coded as per the MedDRA current version.

5.4. Reporting of serious adverse events

5.4.1. Central licensing authority requirements for expedited reporting of SAE

- SAE will be reported by the clinical investigator to sponsor, chairperson of EC and central licensing authority within 24 hours of knowledge of its occurrence.
- Clinical investigator and sponsor will submit a detailed report of SAE to the chairperson of EC, head of the clinical trial site and central licensing authority within 14 days of knowledge of its occurrence.
- IEC will send its review report to the central licensing authority for SAE within 30 days of receiving the report of the serious adverse event from the investigator.
- In case the clinical investigator fails to report any SAE within the stipulated period, he shall furnish the reason for the delay to the satisfaction of the licensing authority along with the report of SAE.
- If applicable, the central licensing authority recommended compensation by order will be paid by the sponsor within 30 days of receipt of such order from the central licensing authority for the SAE that occurred.

All SAEs will be followed up until satisfactory resolution or until the clinical investigator deems the event to be chronic or the volunteer to be stable. Subjects will inform clinical investigators regarding the SAEs (whether related or unrelated) experienced immediately.

SAE will be reported the central licensing authority within 24 hours of its occurrence through online SUGAM portal. SAE will be reported to sponsor and chairman of EC within 24 hours of knowledge of its occurrence on below address:

Table 7: Sponsor and IEC Contact Details

Sponsor's Medical Experts	Independent Ethics Committee
Sponsor's Representative: [redacted]	[redacted]

Pregnancy test will be performed at screening and at visits specified in the protocol.

If a subject becomes pregnant during the study, the subject will be terminated from the study and the event will be handled as per in-house SOP.

6. BIOANALYTICAL PROCEDURES

- Bioanalysis will be carried out for samples from subjects completing the study period.

[redacted]

7. STATISTICAL CONSIDERATIONS

7.1. Pharmacokinetic parameters

The following table represents the PK parameters to be calculated and subjected to statistical analyses.

Table 8: PK Parameters

Primary PK parameters	
C_{max}	Maximum measured plasma concentration of drug
[redacted]	[redacted]

Secondary PK parameters	
$AUC_{0\text{-}inf}$	Area under the plasma concentration versus time curve extrapolated to infinity. $AUC_{0\text{-}inf}$ is calculated as a sum of the $AUC_{0\text{-}t}$ and the ratio of the last measurable plasma concentration to the elimination rate constant, calculated using the formula $AUC_{0\text{-}t} + C_t/K_{el}$. Where C_t is the last measurable drug concentration and K_{el} is the elimination rate constant.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

7.2. Estimation of sample size and justification

A total of 32 + 02 standby*, healthy, adult human subjects will be enrolled in the study.

7.3. Pharmacokinetic analysis

[redacted]

8. DOCUMENTATION

8.1. 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.

8.2. Quality control and quality assurance

Raptim Research Pvt. Ltd., India has a plan in place for the quality of the research being conducted and has standard SOPs for quality management, which describes:

1) How data will be evaluated for compliance with the protocol and for accuracy in relation to source documents.

2) The documents to be reviewed by the Quality Assurance auditor (e.g. CRFs, source documents, product accountability, final study report), who is responsible.

3) The frequency for reviews will be identified in the QA audit plan either in a formal quality management plan or in-house SOPs.

4) Training of the staff on the Protocol requirements by means of classroom/self-reading methods. Methods of training for staff will be specified.

The final report will contain a statement for quality assurance (QA) duly signed by the Head or designated person of quality assurance department.

8.3. Data confidentiality and audits

Subject confidentiality along with the information disclosed/provided/produced by the CRO/sponsor during the clinical study, including, but not limited to, the study protocol, the CRFs, ICFs and results, are strictly held in trust by the sponsor, sponsor's authorized personnel, clinical investigator/clinical co-investigator and their staff members. This confidentiality may extend to cover testing of biological samples in addition to the clinical information relating to participating subjects. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The clinical investigator will permit study-related monitoring, audits and inspections by the IEC, sponsor or its designated study personnel, licensing authority and QA groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.) Further, clinical investigator will allow the auditors or inspectors to have direct access to study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. The confidentiality of the data verified and the protection of the subjects will be respected during these inspections.

9. ETHICAL CONSIDERATIONS

9.1. Ethical conduction and regulatory compliance

The present study will be conducted in accordance with Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects, 64th World Medical

Association – General Assembly, Fortaleza, Brazil, October 2013)1, Good Clinical Practice (International Council for Harmonization – E6 (R2) Guidelines, Current Step 4 Version, dated 9 Nov 2016)2, New Drugs and Clinical trials Rules, 19 March 2019, Ministry of Health and Family Welfare, Government of India3, CDSCO Guidelines for Bioavailability & Bioequivalence Studies Mar 20054, Indian Council of Medical Research (Ethical Guidelines for Biomedical Research on Human Participants, 2017)5 Guidance on the Investigation of Bioequivalence, CHMP – EMA (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**, Jan 2010), ethical requirements of Directive 2001/20/EC[6] and other applicable regulatory requirements.

9.2. Ethics committee approval

The study protocol and related study documents [including English and vernacular informed consent forms (ICFs) and drug related literature] will be reviewed by an IEC. The study will commence only after obtaining the written approval of the study protocol and its related documents by the IEC, with or without modifications.

9.3. Protocol amendments

All protocol amendments, interfering with the subject's health interests and involving changes in the design of the study or its scientific significance will be implemented only after written approval of the Sponsor and IEC. All such changes will be documented in the amended version of protocol and a list of changes with reference to previous version will be generated.

9.4. Informed consent process

[redacted]

[redacted]

[redacted]

10. RECORDING OF DATA, REPORT PREPARATION AND ARCHIVAL

10.1. Record keeping

All clinical record generated during the conduct of the study will be directly entered in CRFs. Data collected on CRFs will be identified by the registration number or subject number and the study code. The Clinical Investigator will abide by the subject confidentiality agreement, except if the information is to be disclosed in assessing the safety of the subject or for regulatory purposes. Data generated during the study will be complied and checked by the clinical investigator or designee for completeness, accuracy, and legibility.

All the bioanalytical data generated during the course of the study will be compiled and to be checked by QA wherever applicable for completeness. Further, the concentration data will be transferred to the statistical department for evaluation.

10.2. Final study report

Final study report will be prepared as per the ICH-E3 guidelines and will be submitted in electronic Common Technical Documentation format including CDISC data14.

10.3. Archival

All the data related to the study will be checked by the archivist as per in-house SOP before archiving.

10.4. Record retention and archiving

All the raw and final data generated in connection with this study and one copy of the final report will be retained at least 2-years after the last approval of a marketing application in an ICH region or as per the Sponsor's requirement (at least 25 years for clinical trial master file and medical file of subject shall be archived in accordance with national law), whichever is earlier.

After the completion of the retention period or the discontinuation of the study, the Sponsor will be notified about the same. If the Sponsor wants to extend the retention of the study documents, then suitable arrangements will be made for the same. The consent from the Sponsor will be taken prior to destruction of any study specific documents.

[redacted]

12. PUBLICATION

The Sponsor will hold the right to publish the results of present study at any time. Any information published will not reveal the identity of the subject and their confidentiality

will be maintained. Clinical Investigator may publish or present the results of this study, in either written or oral format, only after obtaining the written permission of the sponsor.

13. REFERENCES

1. Declaration of Helsinki, Ethical Principles for Medical Research Involving Human Subjects, World Medical Association – General Assembly, Fortaleza, Brazil, October 2013.
2. Good Clinical Practice (International Council for Harmonization – E6 (R2) Guidelines, Current Step 4 version dated 9 November 2016.
3. New Drugs and Clinical trials Rules, 19 March 2019, Ministry of Health and Family Welfare, Government of India[3]
4. Guidelines for Bioavailability and Bioequivalence Studies, CDSCO, Central Drug Standard Control Organization, Directorate General of Health Services, Ministry of Health & Family Welfare, Government of India, New Delhi, March 2005.
5. Ethical Guidelines for Biomedical Research on Human Participants, Indian Council of Medical Research, 2017.
6. Guidance on the Investigation of Bioequivalence, CHMP – EMA (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr**, Jan 2010), ethical requirements of Directive 2001/20/EC.
7. Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies, Dec 2012.
8. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), Guidance for Industry, Bio analytical Method for Validation, Center for Veterinary Medicine (CVM) May 2018.
9. Guidance for industry- Statistical Approaches to Establishing Bioequivalence U.S. Department of Health Services, Food and Drug Administration. Jan 2001.
10. https://www.who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf
11. http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi

[redacted]

14. APPENDICES

Appendix-A: Schedule of Study Events
Appendix-B: Study Specific Requirement

APPENDIX-A: Schedule of Study Events

Procedure	Screening (within 21 days prior to first check-in)	Treatment period Day 0			Post Study (Day 1) OR Withdrawal / termination of a subject
		Check-in (Day 0)	Dosing (Day 1)	Check-out (Day 1)	
[redacted]					

[#]Only during check-in of the period;
[##]Cannula site examination will also be performed.
Note: Screening may be performed on the day of check-in, if required.

APPENDIX-B: STUDY SPECIFIC REQUIREMENT

Sr. No	Section	Remark	Requirements (if yes please specify it)
[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]