Phase III, Randomized, Double-blind, Placebo controlled trial of Efficacy, Safety and Tolerability of Antiviral drug Umifenovir *vs* Standard care of therapy in non-severe COVID-19 patients.

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Table of contents

Table S1. Eight category ordinal scale of WHO extracted for ready reference from

WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis Accessed on 3.6.2020 available at https://www.who.int/blueprint/priority-diseases/key-action/COVID19_Treatment_Trial_Design_Master_Protocol_synopsis_Final_18022020.pdf

Patient Status	**Descriptor**	**Score**
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalised Mild Disease	Hospitalised, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalised Severe Disease	Non-invasive ventilation or high flow oxygen	5
	Intubation and mechanical ventialltion	6
	Ventillation +additional organ support-pressors, RRT, ECMO	7
Dead	Death	8

CONFIDENTIAL

INVESTIGATIONAL NEW DRUG APPLICATION

Umifenovir (Arbidol)

(Antiviral agent)

PROTOCOL FOR PHASE 3 CLINICAL TRIAL & CASE RECORD FORM

Protocol no. CDRI-CLINICAL-2/2020

Version 2 dated

4th June, 2020

The Universal Trial Number (UTN): U1111-1251-8421

Sponsor

COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH-CENTRAL DRUG RESEARCH INSTITUTE

LUCKNOW – 226031

Scientific Title of Study:

Phase 3, Randomized, Double-blind, Placebo control trial of Efficacy, Safety and Tolerability of Antiviral drug Umifenovir vs Standard care of therapy in non-severe COVID-19 patients.

Abbreviated Title: Efficacy and safety study of antiviral Umifenovir therapy in non-severe COVID-19 patients.

Protocol No.: CDRI-CLINICAL2/2020

Version 2 dated 4th June, 2020

The Universal Trial Number (UTN) : U1111-1251-8421

Product: Umifenovir (Arbidol), an antiviral agent

Indication:
COVID-19

Clinical Phase: Phase 3

Clinical Trial Site: Dept. of Meidicine, King George Medical University, Lucknow, RML Institute of Medical Sciences, Lucknow, Era's Lucknow Medical College & Hospital, Lucknow

Sponsor: CSIR-Central Drug Research Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow 226031

Date of Final Protocol: 4th June, 2020

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CERTIFICATE

This is to certify that this document "IND Application of an Efficacy and safety study of antiviral Umifenovir therapy in non-severe COVID-19 patients with protocol number CDRI-CLINICAL2/2020 Version 2 dated 4th June, 2020, has been compiled and verified by undersigned at CSIR-Central Drug Research Institute, Lucknow & King George Medical University, Lucknow.

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COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH

Sponsor Certificate

This is to certify that Phase 3 Clinical Trial with antiviral drug Umifenovir would be fully sponsored by CSIR-CDRI. All the cost including all clinical Trial costs and other research expenses would be borne by CSIR-Central Drug Research Institute, Lucknow.

We also undertake to provide compensation to the clinical trial participants in clinical trial of Efficacy and safety study of antiviral Umifenovir therapy in non-severe COVID-19 patients. The compensation will be given for clinical trial related injury/ death for which these clinical trial participants are entitled to compensation as per Govt. of India Gazette notification vide GSR No. 53(E) dated 30.1.2013 and subsequent amendments as per new drug clinical trials rules dated 19th March 2019.

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"Phase 3, Randomized, Double-blind, Placebo control of Efficacy, Safety and Tolerability of Antiviral Drug Umifenovir vs standard care of therapy in non-severe COVID-19 patients."

6. Commitments:

(i) I have reviewed the clinical protocol and agree that it contains all the necessary information to conduct the study. I will not begin the study until all necessary Ethics Committee and regulatory approvals have been obtained.

(ii) I agree to conduct the study in accordance with the current protocol. I will not implement any deviation from or changes of the protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the Institutional Ethics Committee of the amendment, except where necessary to eliminate an immediate hazard(s) to the trial subjects or when the changes involved are only logistical or administrative in nature.

(iii) I agree to personally conduct or supervise the clinical trial at my site.

(iv) I agree to inform all Subjects; that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent and ethics committee review and approval specified in the New Drugs and Clinical Trials Rules, 2019 and Good Clinical Practices guidelines are met.

(v) I agree to report to the Sponsor all adverse experiences that occur in the course of the investigation(s) in accordance with the regulatory and GCP guidelines.

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(viii) I agree to maintain adequate and accurate records and to make those records available for audit /inspection by the Sponsor, Ethics Committee, Licensing Authority or their authorized representatives, in accordance with regulatory and GCP provisions. I will fully cooperate with any study related audit conducted by regulatory officials or authorized representatives of the Sponsor.

(ix) I agree to promptly report to the Ethics Committee all changes in the clinical trial activities and all unanticipated problems involving risks to human Subjects or others.

(x) I agree to inform all serious adverse events to the Central Licencing Authority, sponsor as well as the ethics committee within twenty-four hours of their occurrence. In case, of failure to do so, I shall furnish the reason for the delay to the satisfaction of the Central Licencing Authority along with the report of the serious adverse event.

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15-05-2020

Signature of Investigator

	Table of Contents	
1.	Title Page	2
2.	Study Contacts	3
3.	Sponsor certificate	6
4.	Undertaking by Investigator	7
5.	Table of Contents	16
6.	List of abbreviations	17
7.	Background and Introduction	18
8.	Preclinical Experience:	19
9.	Study Rationale:	32
10.	Study Objectives:	33
11.	Study Design:	35
12.	Flow Chart of Study	36
13.	Study population:	37
14.	Subject Eligibility: Inclusion Criteria/ Exclusion criteria	38
15.	Study Assessments:	40
16.	Study Conduct:	42
17.	Subject Withdrawals	44
18.	Quality control and Quality assurance	44
19.	Archiving	44
20.	Confidentiality	45
21.	Data handling and management	45
22.	Reporting and Publication	45
23.	Study Treatment:	46
24.	Concomitant Medication:	46
25.	Adverse event monitoring and reporting	46
26.	Subject/Volunteer compensation	48
27.	Ethics: Informed consent, Insurance and Indemnity	49
28.	Study Monitoring and Supervision:	50
29.	Investigational Product management: Storage, Accountability	50
30.	Data analysis	50
31.	References	52
32.	**Appendices**	
33.	Case Record Form	55
34.	Informed Consent Document	71
35.	Bio Data of Investigators	89

LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Explanation
AE	Adverse Event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
AUC0-t	Area under the plasma concentration-time curve from Time zero to time t
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from Time zero to infinity
† b.i.d	bis in die = twice daily
CDC	Centre for Disease Control and Prevention
CK	creatine phosphokinase
Cmax	Maximum (peak) plasma drug concentration
CRF	Case Report Form
COCSS	COVID-19 objective clinical severity score
DSMB	Data Safety and Monitoring Board
ECG	Electrocardiogram
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
Hb	Haemoglobin
Hct	Haematocrit
HDL-C	High Density Lipoprotein –cholesterol
HPLC	High performance liquid chromatography
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IRB	Independent Review Board
LCMS	Liquid chromatography linked mass spectrometry
LDH	Lactate dehydrogenase
LDL-C	Low Density Lipoprotein -cholesterol
MS	Mass spectrometry
MCH	Mean corpuscular haemoglobin
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
ml	milliliter
IEC	Institutional Ethics Committee
RBC	Red Blood Cells
SAE	Serious Adverse Event
SEM	Standard error of the mean
Tmax	Time to reach maximum (peak) plasma concentration
t½	Elimination half-life
WBC	White blood cells

1. Background and Introduction:

Unmet Need: The emergence of SARS-CoV-2 infection, also known as a 2019- nCoV disease (COVID-19), is continuously increasing. The SARS-CoV-2 infection causes a spectrum of respiratory illness, from asymptomatic to fatal pneumonia.[1] The WHO has declared it as pandemic. There is no approved therapy for corona virus disease. There is unmet medical need for newer therapies to reduce morbidity and mortality.

Innovation vis a vis existing therapeutic option:

Currently hydroxychloroquine & lopinavir/ritonavir are used as experimental therapies. However, its effectiveness remains controversial.[2,3] Recently Ministry of Health government of India has issued guidline for treatment of COVID-19 in which hydroxychloroquin with Azithromycin has been mentioned as potential therapy for COVID-19.[4] The different classes of antivirals under evaluation include 3CL protein inhibitors (Ribavirin, Lopinavir/Ritonavir), RNA synthesis inhibitors (Remdesivir, Tenofovir Disoproxil Fumarate/TDF and 3TC), neuraminidase inhibitors (Tamiflu and Peramivir) and other small molecule drugs which target the ability of SARS-CoV-2 to interact with host cells (ACE2 inhibitors).[5] However, the potential drug target and mechanism of several candidate drugs remains elusive and warrants further investigattions.

Umifenovir (also known as Arbidol) is another antiviral agent that has been approved in China and Russia for treating influenza, SARS, and Lassa viruses.[6,7] A limited number of case reports showed that patients with COVID-19 successfully recovered after receiving lopinavir/ritonavir and Umifenovir treatment,[8,9] however, it is difficult to prove whether they were cured by the antiviral agent or just a natural course of COVID-19.[5] Hence further investigation is needed to prove efficacy and safety.

Risk vs Benefit to the patient: The drug Umifenovir is in the market for influenza since years showing its excellent safety profile on human beings. Recently, Xia reported that combination therapy with lopinavir/ritonavir and Umifenovir may likely be preferred in a retrospective study with a small sample size.[10] To date, clinical evidence

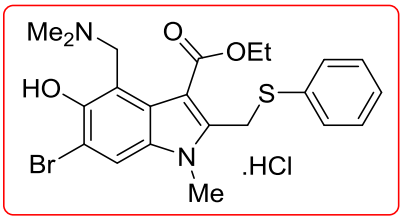
on Umifenovir therapy in patients with COVID-19 is not known. There is no data on Indian patients. Herein, we aim to conduct phase 3 study to find the proof of efficacy of Umifenovir vs standard care of therapy in managing non-severe patients with COVID-19.

Preclincal experience

Umifenovir also known as Arbidol has been marketed for 20 years in Russia and has been used since 2006 in China for the prophylaxis and treatment of human pulmonary diseases caused by influenza A and B viruses and other human pathogenic respiratory viruses.

1. Overview of Umifenovir: history, initial clinical studies in Russia and China, toxicity

Umifenovir or ethyl-6-bromo-4-[(dimethylamino)methyl]-5-hydroxy-1-methyl-2 [(phenylthio)methyl]-indole-3-carboxylate hydrochloride monohydrate, is a small indole derivative.

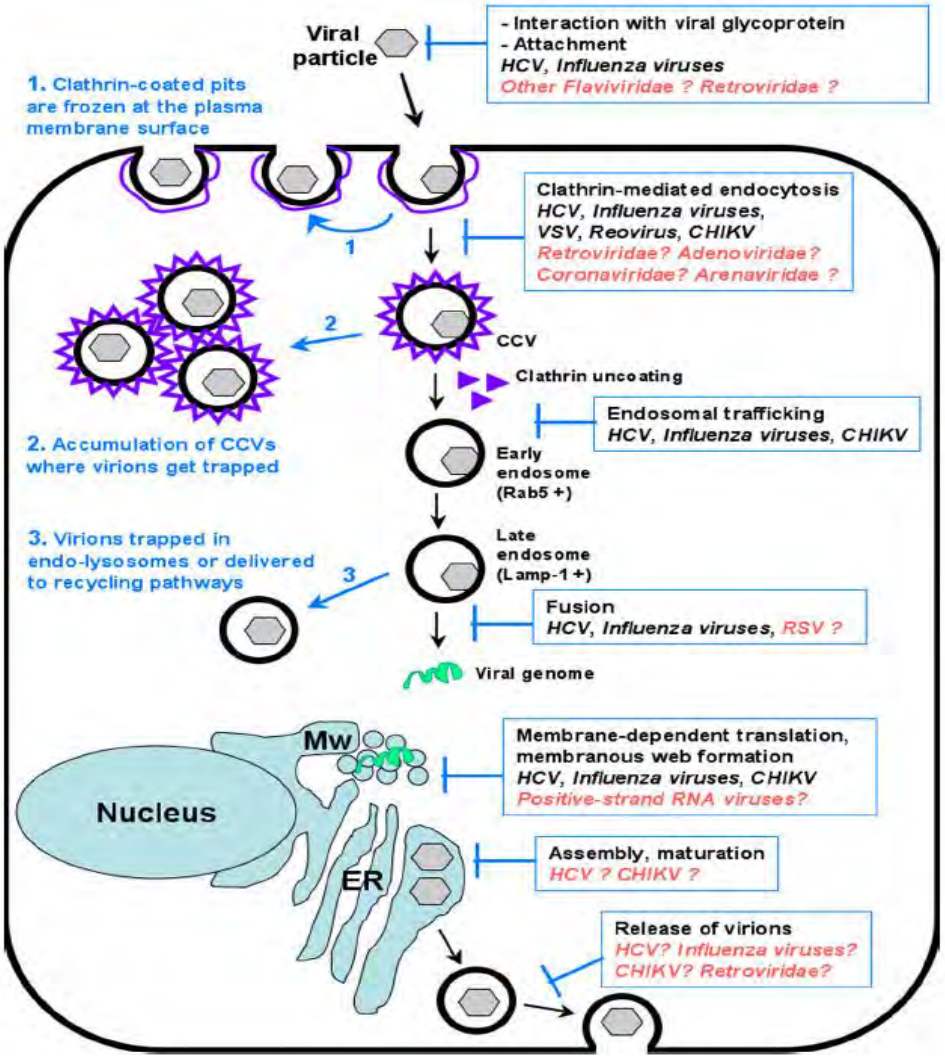


Umifenovir has been shown to display antiviral in vitro and/or in vivo activity against a number of enveloped or non-enveloped RNA or DNA viruses, including influenza viruses A, B and C, respiratory syncytial virus, SARS-CoV, adenovirus, parainfluenza type 5, poliovirus 1, rhinovirus 14, coxsackievirus B5, hantaan virus, Chikungunya virus, HBV and HCV.

Umifenovir broad-spectrum antiviral activity suggests that the molecule acts on common critical step(s) of virus-cell interactions. Evidence indicates that ARB directly exerts a virucidal effect, and can then be considered as a direct-acting antiviral (DAA). Most studies also report an effect of ARB on one or several stages of the viral life cycle, such as cell entry (attachment, internalization) and replication. ARB could

therefore also act as a host-targeting agent (HTA). The following figure explains the actions of drug.[11]

Fig. 1. Broad-spectrum activity of ARB and its molecular mechanisms of action at the cellular level. The different steps of the viral life cycle inhibited by ARB are indicated in blue boxes. Potential effect of ARB on other viruses or families of viruses are mentioned in orange. Blue arrows and text indicate the consequences of ARB on cellular pathways and virions. For clarity and regarding current knowledge about the molecular mechanisms of ARB, we only show the clathrin-dependent endocytosis pathway. MW, membranous web, ER, endoplasmic reticulum.



In view of the in vitro and in vivo data, it is concluded that umifenovir (srbidol) has the ability to elicit protective broad-spectrum antiviral activity against a number of respiratory viruses. Umifenovir may play a significant role in medical countermeasures against respiratory virus infections. All the details are given below.[12]

Table 1. Cytotoxicities of arbidol and ribavirin

Compound	Cell line=CC50(mg=ml)a		
	MDCK	HEp-2	HEL
Arbidol	69.4 ± 8.5	85.4 ± 6.6	72.5 ± 3.2
Ribavirin	232.4 ± 11.6	256.6 ±10.2	189.3 ± 6.8

[a] Mean±S.D. values are shown from three independent experiments. CC50 is the cytotoxic concentration required to reduce the number of viable cells by 50%

Table 2. Antiviral activity of arbidol against different viruses

	IC_{50s}[a] (μg/ml)				
	FLU-A	RSV	HRV 14	CVB3	AdV-7
Drug added before infection	2.7 ± 1.0	8.7 ± 1.4	13.4 ± 1.3	12.7 ± 0.4	NR
Virucidal assay	4.3 ± 0.7	10.4 ± 1.1	13.8 ± 0.4	13.1 ± 0.6	NR
Drug added after infection	9.6 ± 1.0	11.5 ± 1.2	12.5 ± 1.7	9.5 ± 0.6	15.4 ± 0.3

[a] Mean ± S.D. values are shown from three independent experiments.
NR: IC_{50} not reached.
IC_{50} is the inhibitory concentration required to reduce viral replication by 50%.

Table 4. Effect of oral treatment with arbidol in mouse influenza model

Compound	Dosage (mg/kg/day)	Dead/ total	MDD[a] ± S.D.
Arbidol	100	0/10**	>21.0 ± 0.0**
	50	3/10*	9.4 ± 2.9*
	25	5/10	8.6 ± 1.8*
Ribavirin	68	1/10**	12.0 ± 0.0**
Controls[b]	–	8/10	6.4 ± 1.2

[a] Mean day to death of mice dying prior to day 21.
[b] The placebo controls received 0.5% methylcellulose solution instead of the drug.
*$P<0.05$ vs. placebo-treated controls; **$P<0.01$ vs. placebo-treated controls.

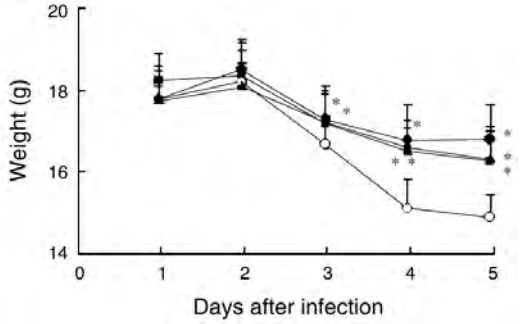


Fig. 1. Effects of orally administered arbidol on weight loss in influenza-virus-infected mice (5–7 weeks old). Mice were infected with influenza virus A/PR/8/34 as described in Materials and Methods. Mice were treated with an oral dose of arbidol of 25 (■), 50 (▲), or 100 (●) mg/kg/day or with 0.5% methylcellulose solution as a control (○) for 6 days beginning 24 h before infection. *$P<0.05$ vs. placebo-treated controls (Student's *t*-test)

Table 5. Effect of oral treatment[a] with arbidol on lung virus yield in mouse influenza model

Group ($n = 8$)	Mean lung parameters[b]	
	Weight (mg ± S.D.)	Virus titer (Log_{10}/lung ± S.D.)
Arbidol at 100 mg/kg/day	122 ± 9**	2.0 ± 0.3**
Arbidol at 50 mg/kg/day	119 ± 8**	2.4 ± 0.2**
Arbidol at 25 mg/kg/day	136 ± 18*	3.2 ± 0.3**
Controls	158 ± 22	4.9 ± 0.1

[a] Treated by oral gavage for 6 days beginning 24 h pre-virus infection.
[b] Mean ± S.D. values are obtained from a single representative experiment.
*$P < 0.05$ vs. placebo-treated controls; **$P < 0.01$ vs. placebo-treated controls.

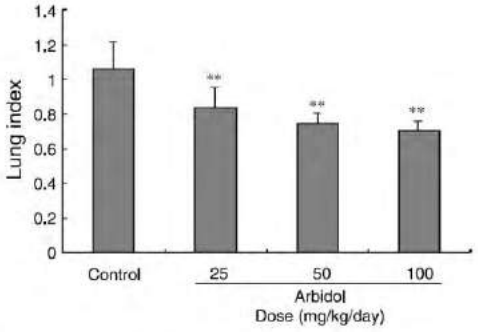


Fig. 2. Effect of oral administration of arbidol on prevention of lung index increase in influenza-virus-infected mice. Mice were infected with influenza virus A/PR/8/34 at 10^5 $TCID_{50}$/mouse, and the lung index was determined as described in Materials and Methods. Mice were treated with an oral dose of arbidol of 25, 50, or 100 mg/kg/day or with 0.5% methylcellulose solution as a control for 6 days beginning 24 h before infection. **$P < 0.01$ compared to the results for placebo-treated controls (Student's t-test)

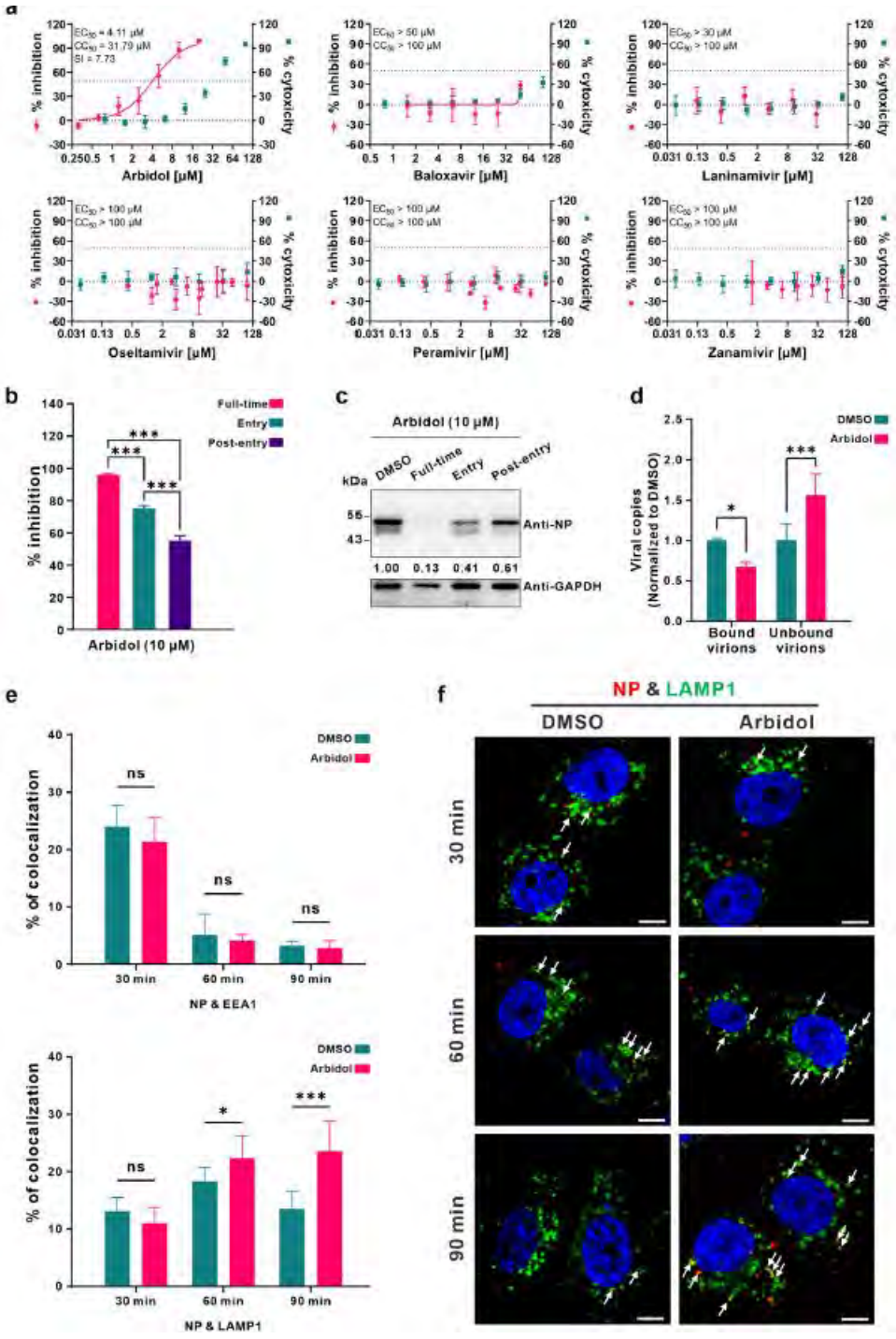
The anti-influenza virus drug, arbidol is an efficient inhibitor of SARS-CoV-2 in vitro[13] (Wang et al. Cell Discovery (2020) 6:28)

In this study, six currently available and licensed anti-influenza drugs were evaluated against SARS-CoV-2. The drugs include arbidol, baloxavir, laninamivir, oseltamivir, peramivir, and zanamivir. The cytotoxicity of the compounds in African green monkey kidney cells, Vero E6 (ATCC-1586) was measured by a standard cell counting kit-8 (CCK8) assay. Then, the cells were infected with SARS-CoV-2 at a multiplicity of infection (MOI) of 0.05 in the presence of either compound or dimethyl sulfoxide (DMSO) control. The dose–response curves were determined by quantification of viral RNA copy numbers in the supernatant of infected cell at 48 h post infection (p.i.). As demonstrated in Fig. 1a, arbidol efficiently inhibited virus infection in vitro. The 50% maximal effective concentration (EC50) and the 50% cytotoxic concentration (CC50) of arbidol was 4.11 (3.55–4.73) and 31.79 (29.89–33.81) μM, respectively, and the selectivity index (SI = CC50/EC50) was 7.73.

Fig.2 Comparative antiviral efficacy of anti-influenza drugs and the mode of actions of arbidol against SARS-CoV-2 infection in vitro.

a. Antiviral activities of the drugs. The antiviral efficacy was evaluated in Vero E6 cells by qRT-PCR analysis of virus yield at 48 h p.i. Data represent the mean ± standard deviation (SD) from two independent repeats. b, c Time-of-addition experiment of arbidol. Three experimental groups (Full-time, Entry, and Post-entry) were set up as described in the Supplementary Methods. At 16 h p.i., virus yield in the cell supernatant was quantified by qRTPCR

(b), and the expression of NP in infected cells was analyzed by western blots (c). The values below the blot represent the relative band intensity (NP/GAPDH) normalized to that of the DMSO group. d Impact of arbidol on SARS-CoV-2 binding. Vero E6 cells were treated with arbidol (10 μM) or DMSO for 1 h prior to infection with SARS-CoV-2 at 4 °C for 1 h. The supernatant (unbound virions) and the cells containing bound virions (bound virions) were collected for quantification of viral RNA copies by qRT-PCR. e, f Effect of arbidol on intracellular trafficking of SARS-CoV-2. The colocalization of virions with EEs or LEs was analyzed by immunofluorescence assays as described in the Supplementary Methods. e The portion of virions that co-localized with EEs or ELs in each group (n > 150 cells) was quantified by Image J. f Representative confocal microscopic images of virions (red) and LAMP1+ ELs (green) in each group. The nuclei (blue) were stained with Hoechst 33258 dye. White arrows: virions co-localized with ELs; bars: 10 μm. For (b) and (e), statistical analysis was performed using a one-way analysis of variance (ANOVA) with GraphPad Prism. For (d), statistical analysis was performed and calculated by unpaired two-tailed t test. *P < 0.05; ***P < 0.001; ns, not significant.


a
% inhibition
% cytoxicity
Arbidol [μM]
Baloxavir [μM]
Laninamivir [μM]
Oseltamivir [μM]
Peramivir [μM]
Zanamivir [μM]
b
Full-time
Entry
Post-entry
% inhibition
Arbidol (10 μM)
c
Arbidol (10 μM)
kDa
DMSO
Full-time
Entry
Post-entry
Anti-NP
Anti-GAPDH
1.00
0.13
0.41
0.61
d
DMSO
Arbidol
Viral copies (Normalized to DMSO)
Bound virions
Unbound virions
e
% of colocalization
ns
30 min
60 min
90 min
NP & EEA1
NP & LAMP1
f
NP & LAMP1
DMSO
Arbidol
30 min
60 min
90 min

Regulatory pharmacology, toxicology and pharmacokinetics

Pharmacokinetics[14]

Arbidol is a broad-spectrum antiviral drug that is used clinically to treat influenza. In this study, the pharmacokinetics, metabolism, and excretion of arbidol were investigated in healthy male Chinese volunteers after a single oral administration of 200 mg of arbidol hydrochloride. A total of 33 arbidol metabolites were identified in human plasma, urine, and feces. The principal biotransformation pathways included sulfoxidation, dimethylamine N-demethylation, glucuronidation, and sulfate conjugation. The major drug-related component in the plasma was sulfinylarbidol (M6-1), followed by unmetabolized arbidol, N-demethylsulfinylarbidol (M5), and sulfonylarbidol (M8). The exposures of M5, M6-1, and M8, as determined by the metabolite-to-parent area under the plasma concentration-time curve from 0 to t (AUC0-t) ratio, were 0.9ı0 .3, 11.5ı 3.6, and 0.5ı0 .2, respectively.

In human urine, glucuronide and sulfate conjugates were detected as the major metabolites, accounting for 6.3% of the dose excreted within 0 to 96 h after drug administration. The fecal specimens mainly contained the unchanged arbidol, accounting for 32.4% of the dose. Microsomal incubation experiments demonstrated that the liver and intestines were the major organs that metabolize arbidol in humans. CYP3A4 was the major isoform involved in arbidol metabolism, whereas the other P450s and flavin-containing monooxygenases (FMOs) played minor roles. These results indicated possible drug interactions between arbidol and CYP3A4 inhibitors and inducers. Further investigations are needed to understand the importance of M6-1 in the efficacy and safety of arbidol, because of its high plasma exposure and long elimination half-life (25.0 h).

Fig 2 Pharmacokinetic parameters of arbidol and its three major metabolites in plasma of four healthy male subjects after a single oral administration of 200 mg of arbidol hydrochloride

Parameter	Value			
	Arbidol	M5	M6-1	M8
T_{max} (h)	1.38 ± 1.11	1.50 ± 1.00	13.0 ± 8.2	19.0 ± 14.0
C_{max} (ng/ml)	467 ± 174	80.5 ± 37.5	525 ± 147	22.7 ± 9.8
AUC_{0-t} ($ng \cdot h \cdot ml^{-1}$)	2,103 ± 614	1,743 ± 466	23,104 ± 4,829	1,040 ± 483
$AUC_{0-\infty}$ ($ng \cdot h \cdot ml^{-1}$)	2,203 ± 691	2,121 ± 546	28,399 ± 7,656	1,315 ± 561
$t_{1/2}$ (h)	15.7 ± 3.8	26.3 ± 5.9	25.0 ± 5.4	25.7 ± 8.8
CL/F (liters/h)	99 ± 34			

Adapted from Antimicrobial Agents and Chemotherapy April 2013 Volume 57 Number 4 p. 1743–1755.

Pharmacokinetics of single and multiple oral doses of arbidol in healthy Chinese volunteers. [16]

Background: Arbidol is licensed in Russia and China for prophylaxis and treatment of influenza A and B. This study was to assess the pharmacokinetics of single and multiple doses of arbidol in healthy Chinese volunteers. Methods: This was a single-center, open-label, two-phase study conducted in 12 subjects. In singledose phase, subjects were randomized to receive single doses of 0.2, 0.4 and 0.8 g of arbidol in a crossover design with a 7-day washout period between administration. In the multiple-dose phase, subjects received 0.2 g 3 times a day for 7 days. Serial blood samples were collected at predefined time points. Plasma concentrations were determined with a validated HPLC method. Safety assessments were conducted throughout the study. Results: After administration of single doses of 0.2, 0.4 and 0.8 g, geometric mean estimates for arbidol Cmax were 0.70, 1.24, and 2.16 mg/l and the mean of AUClast were 3.27, 5.81 and 12.72 mg×h/l, respectively. The AUClast and Cmax showed dose proportionality. After administration of multiple doses, the mean of Cmax,ss of arbidol was 0.41 mg/l and the mean accumulation ratio is ~ 1.12. Compared with single-dose phase, arbidol exhibited lower Cmax and prolonged plasma concentration profiles. Conclusions: In healthy Chinese subjects, single dosing of arbidol resulted in linear plasma pharmacokinetics. Arbidol exhibited little accumulation with repeated

administration. Compared with single doses, multiple oral doses showed somewhat different pharmacokinetics and tissue distribution patterns. Sex did not appear to affect the pharmacokinetic properties of arbidol.

Toxicity

Toxicity of the preparation of "arbidol" with v/zh introduction to the male rats shows following results.

LD50 = of 5200 B± 350 mg/kg

LD16 = of 3800 B± 250 mg/kg

LD84 = of 7100 B± 400 mg/kg

Repeat Dose Toxicity Studies:

It is established that the application of preparation of "arbidol" (Umifenovir) in rats at doses 50 and 500 mg/kg for a period of 130 days does not lead to lethality and development of the irreversible pathologic changes (T.A. Of gus'kova. Toxicology of medicines. M., "Russian doctor", 2003, s. 103).

Embryotoxicity Studies:

Study of the embryotoxic action of the preparation Of "arbidol" on the white low breed rats with the introduction at doses 50 and 500 mg/kg from the 1st through the 19th the days of the pregnancy

Saftey Pharmacology: Umifenovir is found safe in safety pharmacology studies and do not have negative effect of cardiovascular, respiratory, and central nervous system (source L China drug magazine 2006 14 , available at www.Arbidol.com). The abstract is given below

Arbidol Objective: To evaluate the effects on the central nervous system, cardiovascular system and respiratory effects. Methods : Observation ig given Arbidol hydrochloride (10,50 and 250 mg · kg-1) in mice generally, loss of righting reflex, spontaneous activity, sensory and memory, sleep-induced; Observation ig given

Arbidol hydrochloride (10, 30 and 90 mg · kg-1) changes in the temperature of rabbits; Observation ig given Arbidol hydrochloride (20 and 80 mg · kg-1) in anesthetized dogs breathing frequency and amplitude. systolic and diastolic blood pressure, heart rate and rhythm, a QRS ECG T-wave, PR interval, and ST segment affected.

Results : ig mice Arbidol hydrochloride (250 mg kg), a synergistic effect of sodium pentobarbital-induced sleep. The remaining parameters were not significantly affected.

CONCLUSION : Arbidol effects on the central nervous system. no effect on the cardiovascular and respiratory systems.

Clinical Experience;

Two faviurable clinical study results are published for use of Umifenovir in CoVID-19. The other clinical trials are ongoing. The results published by Deng Li and Xia showed that Umifenovir treatment when combined with Lopinavir/Ritonavir (LPV/r) is beneficial and shows 75% patient responded to Umifenovir , LPV/r combination therapy as compared to 35% LPV/r monotherapy on day seven. [10]

The another study by Z. Zhu et al concluded that Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19.[15]

The study was also performed comparing effects of Favipiravir versus Arbidol for COVID-19 in 240 patients by Chen et al. [16] The study showed that there is no difference in clinical recovery rate at day 7 between two groups.

The abstracts are given below

i) Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study.

BACKGROUND:

Corona Virus Disease 2019 (COVID-19) due to the 2019 novel coronavirus (SARS-CoV-2) emerged in Wuhan city and rapidly spread throughout China. We aimed to compare arbidol and lopinavir/ritonavir(LPV/r) treatment for patients with COVID-19

with LPV/r only.

METHODS:

In this retrospective cohort study, we included adults (age≥18years) with laboratory-confirmed COVID-19 without Invasive ventilation, diagnosed between Jan 17, 2020, and Feb 13, 2020. Patients, diagnosed after Jan 17, 2020, were given oral arbidol and LPV/r in the combination group and oral LPV/r only in the monotherapy group for 5-21 days. The primary endpoint was a negative conversion rate of coronavirus from the date of COVID-19 diagnosis(day7, day14), and assessed whether the pneumonia was progressing or improving by chest CT (day7).

RESULTS:

We analyzed 16 patients who received oral arbidol and LPV/r in the combination group and 17 who oral LPV/r only in the monotherapy group, and both initiated after diagnosis. Baseline clinical, laboratory, and chest CT characteristics were similar between groups. The SARS-CoV-2 could not be detected for 12(75%) of 16 patients' nasopharyngeal specimens in the combination group after seven days, compared with 6 (35%) of 17 in the monotherapy group ($p < 0{\cdot}05$). After 14 days, 15 (94%) of 16 and 9 (52·9%) of 17, respectively, SARS-CoV-2 could not be detected ($p < 0{\cdot}05$). The chest CT scans were improving for 11(69%) of 16 patients in the combination group after seven days, compared with 5(29%) of 17 in the monotherapy group ($p < 0{\cdot}05$).

CONCLUSION:

In patients with COVID-19, the apparent favorable clinical response with arbidol and LPV/r supports further LPV/r only.

(Deng L, Li C, Zeng Q, Liu X, Li X, Zhang H, Hong Z, Xia J, Arbidol combined with LPV/r versus LPV/r alone against Corona Virus Disease 2019: A retrospective cohort study. J Infect. 2020 Mar 11. pii: S0163-4453(20)30113-4. doi: 10.1016/j.jinf.2020.03.002.)

ii) Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19

Lopinavir/ritonavir and arbidol have been previously used to treat acute respiratory syndrome- coron- avirus 2 (SARS-CoV-2) replication in clinical practice; nevertheless,

their effectiveness remains controver- sial. In this study, we evaluated the antiviral effects and safety of lopinavir/ritonavir and arbidol in pa- tients with the 2019-nCoV disease (COVID-19). Fifty patients with laboratory-confirmed COVID-19 were divided into two groups: including lopinavir/ritonavir group (34 cases) and arbidol group (16 cases). Lopinavir/ritonavir group received 400 mg/100mg of Lopinavir/ritonavir, twice a day for a week, while the arbidol group was given 0.2 g arbidol, three times a day. Data from these patients were retrospec- tively analyzed. The cycle threshold values of open reading frame 1ab and nucleocapsid genes by RT- PCR assay were monitored during antiviral therapy. None of the patients developed severe pneumonia or ARDS. There was no difference in fever duration between the two groups ($P = 0.61$). On day 14 after the admission, no viral load was detected in arbidol group, but the viral load was found in 15(44.1%) patients treated with lopinavir/ritonavir. Patients in the arbidol group had a shorter duration of positive RNA test compared to those in the lopinavir/ritonavir group ($P < 0.01$). Moreover, no apparent side effects were found in both groups. In conclusion, our data indicate that arbidol monotherapy may be superior to lopinavir/ritonavir in treating COVID-19.

(Z. Zhu, Z. Lu and T. Xu et al., Arbidol monotherapy is superior to lopinavir/ritonavir in treating COVID-19, Journal ofInfection, https://doi.org/10.1016/j.jinf.2020.03.060)

Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial

Abstract

Background : No clinically proven effective antiviral strategy exists for the epidemic Coronavirus Disease 2019 (COVID-19).

Methods: We conducted a prospective, randomized, controlled, open-label multicenter trial involving adult patients with COVID-19. Patients were randomly assigned in a 1:1 ratio to receive conventional therapy plus Umifenovir (Arbidol) (200mg*3/day) or Favipiravir (1600mg*2/first day followed by 600mg*2/day) for 10 days. The primary outcome was clinical recovery rate of Day 7. Latency to relief for pyrexia and cough, the rate of auxiliary oxygen therapy (AOT) or noninvasive mechanical ventilation (NMV) were the secondary outcomes. Safety data were collected for 17 days.

Results: 240 enrolled COVID-19 patients underwent randomization; 120 patients were assigned to receive Favipiravir (116 assessed), and 120 to receive Arbidol (120 assessed). Clinical recovery rate of Day 7 does not significantly differ between Favipiravir group (71/116) and Arbidol group (62/120) (P=0.1396, difference of recovery rate: 0.0954; 95% CI: -0.0305 to 0.2213). Favipiravir led to shorter latencies to relief for both pyrexia (difference: 1.70 days, P<0.0001) and cough (difference: 1.75 days, P<0.0001). No difference was observed of AOT or NMV rate (both P>0.05). The most frequently observed Favipiravir-associated adverse event was raised serum uric acid (16/116, OR: 5.52, P=0.0014).

Conclusions: Among patients with COVID-19, Favipiravir, compared to Arbidol, did not significantly improve the clinically recovery rate at Day 7. Favipiravir significantly improved the latency to relief for pyrexia and cough. Adverse effects caused Favipiravir are mild and manageable. This trial is registered with Chictr.org.cn (ChiCTR2000030254).

2. Study Rationale:

Umifenovir is another antiviral agent that has been approved in China and Russia for treating influenza, SARS, and Lassa viruses.[6,7] A limited number of case reports showed that patients with COVID-19 successfully recovered after receiving lopinavir/ritonavir and Umifenovir treatment [8,9] ; however, it is difficult to prove whether they were cured by the antiviral agent or just a natural course of COVID-19.[5] Recently, Xia reported that combination therapy with lopinavir/ritonavir and Umifenovir may likely be preferred in a retrospective study with a small sample size.[10] To date, clinical evidence on Umifenovir therapy on Indian patients with COVID-19 is not known. Herein, we aim to conduct phase 3 study to find the efficacy of Umifenovir vs standard care of therapy in managing non-severe patients with COVID-19.

Dosages in study will be Umifenovir 800mg twice daily for 14 days + standard care of therapy. As per the pharmacokinetic study,[17] the drug Umifenovir 800mg achives sufficient concentration to inhibit the the virus SARS-COV2. The drug has half life of about 12-16 hours so can be administered twice daily.

The standard care of therapy is as per the hospital protocol and as per Ministry of Health, Govt. of India COVID-19 treatment guidelines adopted by trial centre.

3. Study Objectives:

To assess the efficacy, safety and tolerability of Umifenovir in corona virus disease (COVID-19) patients.

Primary outcome measures

- Time from randomization to nasopharyngeal swab negativity by two RT-PCR tests, for SARS-Cov-2 antigens, taken 24 hours apart.
- For moderate patients, the end point will be time to improvement by one category from randomisation on the eight-category ordinal scale defined by WHO[19] & average change in the ordinal scale from baseline.

Secondary outcome measures

- Time from randomization to clinical recovery or deterioration, assessed at 0, 7, 14, 21 and 28 days, on eight-category ordinal scale defined by WHO[19] consisting of the following categories:

Patient Status	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalised Mild Disease	Hospitalised, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalised Severe Disease	Non-invasive ventilation or high flow oxygen	5
	Intubation and mechanical ventialltion	6
	Ventillation +additional	7

	organ support- pressors, RRT, ECMO	
Dead	Death	8

- Proportion of patients to clinical recovery or deterioration, assessed at 0, 7, 14, 21 and 28 days, on eight-category ordinal scale defined by WHO[19] consisting of the following categories:
- Proportion of patients hospitalized with Severe Covid-19 pnemonia (with respiratory rate ≥30/minute and/or SpO2 < 90% in room air) or ARDS or Septic shockas per Ministry of health, Govt of India guidelines.
- Adverse events in two groups.

4. Study Design:

- Study Type: Interventional (Clinical Trial)
- Actual Enrollment: Total 132. (Two arm study, 66 patients in each arm)
- Allocation: Computerised Randomization. Sequentially numbered, opaque, sealed envelopes (**SNOSE**)
- Intervention Model: Parallel Assignment
- Masking: Double-blinded placebo controlled
- Primary Purpose: Treatment
- No. of centres Three. Multicentric study
- Duration of study: Subject will be observed upto 28 dyas
- Type of study/Title: Phase 3, Randomized, Double-blind, Placebo control trial of Efficacy, Safety and Tolerability of Antiviral drug Umifenovir vs Standard care of therapy in non-severe COVID-19 patients.

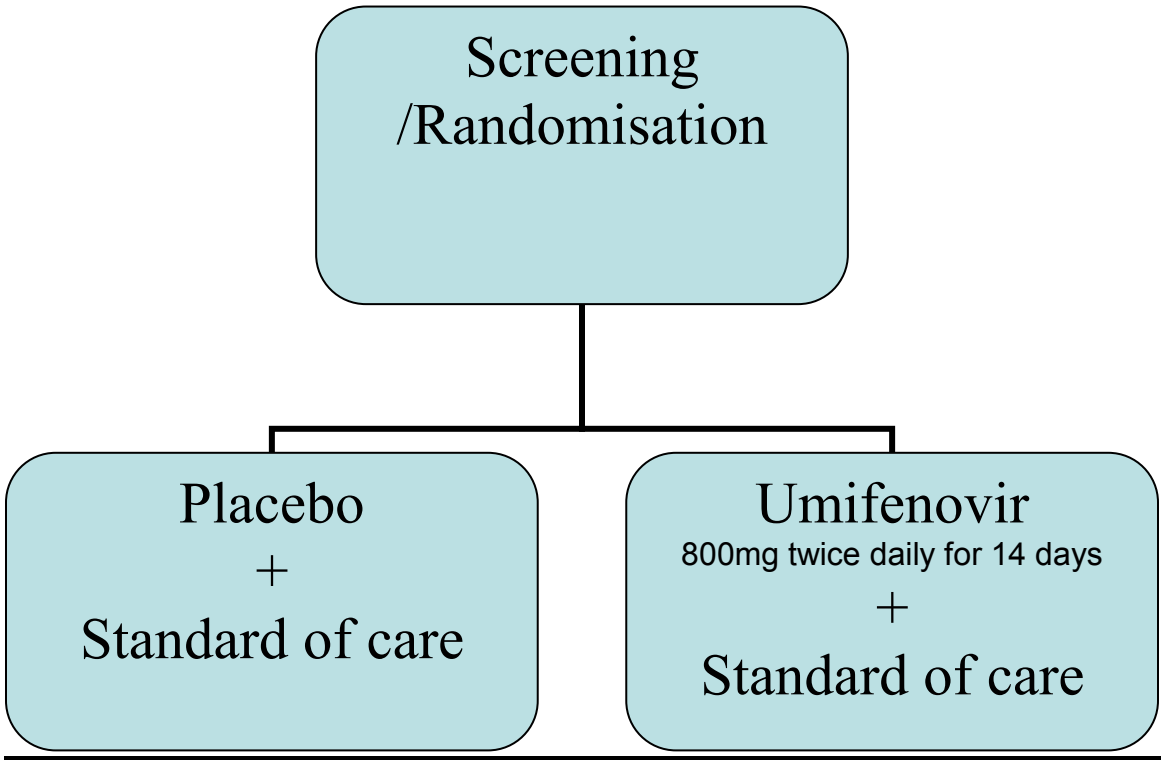
a) The study will be conducted at King George Medical University, Lucknow, ERAs Medical College, Lucknow and Ram Manohar Lohia hospital Lucknow.

b) Allocation to treatment will be according to a predetermined random order. Randomization of Umifenovir or placebo will take place for each group separately. The randomization list will be generated using computer program of randomization and will be stritificaly randomized to have sufficient number of patients of asymptomatic, mild and moderate patients. The allocation concealment will be maintained using opaque envelopes.

Arms and Interventions

- Arm 1: Umifenovir 800mg twice daily for 14 days + standard care of therapy.
- Arm 2: Standard care of therapy
- The standard care of therapy is as per the hospital protocol and as per Ministry of Health, Govt. of India COVID-19 treament guidelines adopted by trial centre.

- **Flow Chart of Phase 3 Study**



5. Study population:

The patients visiting OPD/IPD of King George Medical University, Lucknow, Era Medical college Lucknow & Ram manohar Lohia hospital Lucknow will be recruited from the study. The number of participants will be 66 in each arm. Total 132 patients.

Number of subjects: 66 patients in each arm (132 patients in total)

The sample size of the present study is based on primary outcome measure i.e. nasopharyngeal swab negativity by RT-PCR test. Sample size estimation is based on assumption that the average time (duration) of discharge of patient in SOC group be 13± 2.5 days. For any patient to be discharged in lesser time than 11.7 days we require sample size to be calculated by

$$\eta = 2.(Z\alpha/2 + Z\beta)2\ \sigma 2 / (x1 - x2)2$$

Where $Z\alpha/2 = 1.96$ level of significance, $Z\beta = 0.842$ power of test= 80%, x1 = 11.7 days, x2 = 13 days, (x1 - x2) = 1.3, $\sigma = 2.5$ days, x1 - x2 the minimum time difference which can be significant.

$$\eta = 2\times (1.96 + 0.842)2 \times 2.52 /1.32$$
$$= 2 \times (2.802) \times 6.25/1.69$$
$$= 58.1 = 58$$

It gives $\eta = 58$, With 10% margin of dropouts the required sample size would be

n = 58 + 10% of 58 = 64

Since the randomization sequence shall move in blocks of 6, a sample size of 66 has been finalized to represent each arm appropriately.

6. Subject Eligibility:

The participants will be recruited in the study by physical and laboratory examination.

- **Inclusion Criteria:**

o **Asymptomatic** persons aged 18-75 years (inclusive), at the time of signing the Informed Consent Form (ICF), WITH Nasopharyngeal swab positivity in RT-PCR tests for SARS-Cov-2 antigens detected during screening of contacts or sentinel surveillance shall be defined as asymptomatic cases. The aymptomatic individuals are persons without COVID -19 symptoms as defined in Ministry of Health & Family welfare, Govt. of India guidelines.

o Case categories according to severity as per Ministry of health & Family welfare, Govt of India guidelines:

- Uncomplicated illness: Patients with uncomplicated upper respiratory tract viral infection may have non-specific symptoms such as fever, cough, expectoration, shortness of breath, myalgia, fatigue, sore throat, nasal congestion, diarrhea, loss of taste WITH Nasopharyngeal swab positivity in RT-PCR tests for SARS-Cov-2 antigens.
- Mild pneumonia WITH Nasopharyngeal swab positivity in RT-PCR tests for SARS-Cov-2 antigens.
- Moderate pneumonia WITH Nasopharyngeal swab positivity in RT-PCR tests Moderate disease is considered as Pneumonia with no signs of severe disease. Adults with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 <94% (range 90-94%) on room air, Respiratory Rate more or equal to 24 per minute.

o Additional Inclusion Criteria

a) For mild cases: The interval between symptoms onset (or day of contact with a COVID-19 for asymptomatic patients detected during surveillance) and randomization is no more than 7 days.

b) For moderate cases: The interval between symptoms onset (or day of contact with a COVID-19 for asymptomatic patients detected during surveillance) and randomization is no more than 12 days.

o Eligible subjects of child-bearing age (male or female) must agree to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) with his/her partner during the study period.

o Not participating in any other interventional drug clinical studies before completion of the present study.

- **Exclusion Criteria:**

- Severe COVID-19, as defined in Ministry of Health, Govt of India guidelines. Adolescent or adult: fever or suspected respiratory infection, plus one of the following; respiratory rate >30 breaths/min, severe respiratory distress, SpO2 <90% on room air, Cases of Acute respiratory distress syndrome (ARDS).
- Sepsis, Septic shock as defined in MOH&FW guidelines. The cases as need for invasive or non-invasive ventilator support, ECMO or shock requiring vasopressor support. Inability to intake or tolerate oral medications.

o Known allergy or hypersensitivity to Umifenovir

o Possibility of the subject being transferred to a non-study hospital within 72h

o Pregnant or lactating women

o Severe liver disease: underlying liver cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the ULN;

o Known severe renal impairment [creatinine clearance (CcCl) <30 mL/min] or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis.

O Known disease or comorbid condition like asthma, diabetes with second-and third-line medicines, insulin as defined in WHO guidance document.[18]

O The disease or condition which may affect the study as decided by physician.

5. Study Assessments:

- Patients attending the fever clinic, or those admitted to the trial/isolation unit of Department of Infectious Diseases, King George's Medical University, Lucknow, Era's medical College, Lucknow, Ram manohar Lohia institute of medical Sciences, Lucknow and detected positive shall be enrolled in the trial.
- The nasopharyngeal swabs shall be collected on days 0, 5, 7, 9, 11, 13, 15, 17, 19, 21 and 28.
- The severity of COVID-19 shall be assessed as per Minsitry of health, Govt. of India guidelines; those with mild to moderate disease shall be screened further while those with severe disease shall be excluded.
- Cases categorized as asymptomatic shall be constituted by positive contacts of the COVID-19 positive patients or those detected through sentinel surveillance or screening, but showing no COVID-19 related symptoms.
- The bioanalytical facilities at CSIR-Central Drug Research Institute, Lucknow and Department of Microbiology, KGMU and respective clinical trial sites shall be used to perform all the assessments.
- Complete blood count, liver function tests, renal function tests with electrolytes, fasting blood sugar, thyroid function test, glycosylated hemoglobin, urine examination, electrocardiogram, coagulation profile, and chest X-Ray shall be done in all cases. CECT (Chest) shall be done, as required. The frequency of each investigation has been detailed in **Table 1**.

Table 1: Timings of assessment of various parameters during the trial period

Parameters	Timings of various assessments (days)						
Study Stage	**0**	**3**	**5**	**7**	**14**	**21**	**28**
Informed Consent Form	x						
Demographics	x						
Physical Examination	x	x	x	x	x	x	x
Review of Inclusion/ exclusion criteria	x			x	x		
CBC	x			x	x	x	x
ESR	x			x	x	x	x
Quantitative CRP	x			x	x	x	x
ABG + (As & when required)	x			x	x		
Serum Ferritin	x			x	x	x	x
Urine Routine	x			x	x	x	x
LFT	x			x	x	x	x
KFT	x			x	x	x	x
Serum Sugar fasting PP + as required	x						
Glycosylated haemoglobin	x						
Coagulation profile	x			x	x		x
Tri glycerides	x			x	x		x
Chest Imaging X-Ray/CT	x			x	x	x	x
ECG	x	x	x	x	x	x	x
Pregnancy Test	x						
Trial drug Dispensing	x			x			
Administration Record of Clinical treatment scheme	x	x	x	x	x	x	x
Adverse Events	x	x	x	x	x	x	x

Nasopharyngeal Swab	Day 5	Day 7	Day 9	Day 11	Day 13	Day 15	Day 17	Day 19	Day 21	Day 28

Note: Fever charting, blood pressure monitoring, assessment of hydration, and oxygenation shall be done twice a day or as clinically indicated.

8. Study Conduct:

Screening and Informed Consent (Visit 1)

A screening/baseline will be performed prior to the enrollment into the study. At the screening visit, subjects will be approached to obtain written informed consent prior to any study specific procedures being performed. The purpose of the study and the benefits and risks of the procedures will be explained to the subject and the consent process must be documented accordingly in the medical record. Subjects who agree to study participation must sign an IRB-approved ICF. Subjects will be informed that their participation in this study is voluntary and they may refuse to participate or discontinue from the study at any time. Subjects will be given the opportunity to ask the investigator questions so that they are adequately informed about the research. A copy of the signed informed consent must be provided to the subject and the informed consent process will be documented in source documents. If new information becomes available that may affect a subject's decision to continue to take part in the study, this information will be discussed with the subject by the investigator.

The following assessments will be performed prior to the scheduled procedure and the results recorded on the appropriate subject CRFs:

- Verification of eligibility criteria and subject risk per guidelines
- Demographics (age, gender, height, weight)
- Surgical and medical history (prior abdominal surgery, GI symptoms)
- General medical history will be assessed based on the subject's clinical condition

Recruitment visit (Day1)

Patients who are tested positive for COVID-19 and who need further workup for laborartory examination will be assessed and enrolled into the the study. Patients who were found to be not eligible for the study following signature of the Informed Consent Form will be withdrawn from the study. The screening and recruitment may be done in same visit if all reports are available.

The randomization was done as per computer randomization. The randomization will be stratified randomization giving sufficiant number of patient in subgroups like

asymptomatic, mild & moderate. The Randomization wiil be done as per the sealed envelop received from sponsor.

Investigational drug Umifenovir/Placebo for seven days at time will be dispensed to volunteer to complete the fourteen days therapy. All records will be maintained by investigator.

Study visits: Nasopharyngeal swab will tested after screening and randomization for day 5, 7, 9,11,13,15,17,19,21,28.

Visit for Day 3: Subject will be clinically examined and also will be looked for any adverse event as per study procedures. ECG will be done.

Visit for Day 5: Subject will be clinically examined. The subject will be also assessed for hematology and biochemistry and other investigations as per table 1 (page 41). ECG will be done.

Visit for Day 7: Subject will be clinically examined. The subject will be also assessed for hematology and biochemistry and other investigations as per table 1 (page 41). ECG and X ray will be done.

Visit for Day 14: Subject will be clinically examined. The subject will be also assessed for hematology and biochemistry and other investigations as per table 1 (page 41). ECG and X ray will be done. Investigational drug therapy will be discontinued and subject will be called for follow up

Visit for Day 21: (Follow up visit) Subject will be clinically examined. The subject will be also assessed for hematology and biochemistry and other investigations as per table 1 (page 41). ECG and X ray will be done.

Visit for Day 28: (Follow up visit) Subject will be clinically examined. The subject will be also assessed for hematology and biochemistry and other investigations as per table 1 (page 41). ECG and X ray will be done.

The subject wil be given standard of care as per hospital procedures. The treatment will be decided by physician which will not affect study. The adverse event monitoring will be done. Subject will informed that he can approach at any time in case of emergency. In emergency or any complications, subject will be admitted and treated.

Subject Withdrawals/ Discontinued subjects

A subject may withdraw for any reason. The Investigator will advise the Sponsor of the withdrawal of any subject. The subject who tested negative after treatment will not undergo further assessment of testing. He will do visits for clinical examination only and will not be considered as dropouts. A subject may be withdrawn in any of the following circumstances:

Serious Adverse Events, Protocol violation; Withdrawal of consent; Termination of the study by the Investigator or Sponsor.

Subjects who voluntarily withdraw are termed dropouts.

If a. subject is withdrawn due to an Adverse Event, appropriate medical care will be provided and the Adverse Event should be followed to resolution. Follow-up procedures should be conducted as scheduled. The person can visit at any day in case of emergency.

Quality control and Quality assurance

The principal investigators will maintain quality assurance and quality control systems to ensure that the trial is conducted and data generated, recorded and reported in compliance with the protocol, Good Clinical Practice guidelines and the applicable regulatory requirements. Personal subject data will be kept confidential. Internal and external quality control will be carried out for all laboratory tests. Authorized representatives of sponsor or a regulatory authority may perform audits or inspections at the centre, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, The investigator will contact sponsor immediately if contacted by a regulatory agency about an inspection at the centre.

Archiving

The principal investigator will arrange for the retention of the subject identification list for at least 15 years after completion or discontinuation of the trial. The investigator will also retain the subject files and source documents for 10 years. The Central Drug

Research Institute will inform the investigator when the documents no longer need to be retained.

Confidentiality

The results of the study and the details of subject/volunteer participation will be kept strictly confidential. However, the information regarding the study will be made known to the clinical monitor and regulatory authorities.

Data handling and management

All trial data will be recorded directly on the case record forms supplied by the Central Drug Research Institute. Only the investigators and authorized co-workers are permitted to make entries in the CRFs. After completion of the CRFs, the investigator will scrutinize the CRFs for completeness and accuracy. Statistical analysis will be done after all verification and the data has been locked.

Reporting and Publication

This will be the joint responsibility of the CSIR-Central Drug Research Institute and the principal investigators, both of whom will agree upon the final manuscript. CSIR-Central Drug Research Institute will send the manuscript for publication.

9. Study Treatment: The volunteers will receive study as drug as per the randomaly assigned treatment either in a group.

Arms and Interventions

- **Arm 1: Umifenovir 800mg twice daily for 14 days + standard care of therapy.**
- **Arm 2: Standard care of therapy**
- **The standard care of therapy is as per the hospital protocol and as per Ministry of Health, Govt. of India COVID-19 treatment guidelines adopted by trial centre.**

Concomitant Medication: No concomitant medication is allowed apart from standard of care and investigational drugs as per the protocol. The physiscian will decide and drug which may interfere with the Umifenovir and it should not be allowed. If the volunteers need any treatment which may affect study, he will be given treatment immediately and sponsor will be consulted for discontinuing volunteer from this study.

Adverse event monitoring and reporting

Each subject will be carefully monitored for adverse events. This includes clinical and laboratory test variables. An assessment will be made of seriousness and intensity.

Severity of adverse events Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 will be used

The following classification will be used

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 ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE. Adverse event documentation

All adverse events occurring during the trial and follow up period will be fully recorded in CRF. Each event will be documented in detail along with start and stop dates, intensity, relationship to investigational product, action taken and outcome.

Reporting of serious adverse events

All SAEs occurring after randomization will be reported within 24 hours of awareness, to the DCGI, CDRI (Sponsor), and ethics committee independent of the relationship of the study product.

Reporting procedures for all SAEs will be followed as per Drugs and Cosmetics (First Amendment) Rules,2013,122-DAB, new drug clinical trial rules and application amendments there of. Copies of each report and documentation of IEC/IRB notification and receipt will be kept in the Site Trial Master File.

The minimum information required for the initial SAE report is:

- Identifiable Subject
- Suspect Medicinal Product
- Identifiable reporting source and
- An event or outcome that can be identified as SAE

All actions taken by the investigator and the outcome of the event will be reported immediately. For documentation of the SAEs and, any actions taken, for outcome and follow-up reports the SAE report forms will be used. Where applicable, hospital case records, and autopsy reports (including verbal autopsy) will be obtained.

Reporting by the Sponsor[CDRI]

All SAEs after randomization will be reported within 24 hours of awareness, to the DCGI and the ethics committee that accorded approval to the study. Reporting procedures for all the SAEs will be followed as per Drugs and Cosmetics (First Amendment) Rules,2013,122-DAB and applicable amendments thereof.

If a previous AE that was not initially deemed reportable is later found to fit the criteria for SAE reporting, the study sponsor will submit the SAE in a written report to the DCGI per current regulations, using the date of determination the vent has become an SAE as the reference date for the reporting deadline.

Reporting by the ethics committee

Reporting procedures for all the SAEs will be followed as per the Drugs and Cosmetics (First Amendment) Rules ,2013,122-DAB and New drug clinical trial rules 2019 applicable amendments thereof.

Treatment and follow up of Serious Adverse Events

All SAEs will be followed up until resolution, until the condition stabilizes, until the event is otherwise explained, or until the subject is lost to follow-up, whichever is earlier. Reports relative to the subsequent course of the SAE noted for any subject must be submitted to the sponsor. The sponsor will provide medical management in case of any injury to clinical trial subjects in compliance with "Drugs and Cosmetics (First Amendment) Rules,2013,122-DAB: compensation in case of injury or death during clinical trials" and applicable amendments thereof.

Dose Modification

Participants who experience unacceptable AEs attributed to the study product should not receive any further doses and should be treated at the investigator's discretion.

Subject/Volunteer compensation

The participation of the subject/volunteers is of their own free will. However, for the inconvenience of drug administration and blood collections, they will receive compensation as per the usual norms of the institution. It has been decided to pay appropriate amount as detailed in the patient information sheet. This is based on the number of days a person stays in the unit, the number of visits he makes, the number of blood samples withdrawn and the inconvenience. This compensation will be entered on the subject information sheet and informed consent form and will also be sent to the

ethical committee for approval. In the event of SAE, the compensation to the participant will be provided as per the rule ”122-DAB-compensation in case of injury or death during clinical trials” in notification released by Ministry of Health and Family Welfare on 15th December 2014 of recent amendments in the New drug clinical trial rules 2019 or more current information provided by ministry of Health and Family Welfare, as applicable.

11. Ethics:

The study will be initiated after approval from the Drugs Controller General of India and the institutional ethics committees of KGMU Lucknow and respective ethics committee at each centre in RML hospital lucknow and Era Medical college lucknow. The study will be conducted as per GCP guidelines. The study will be enrolled in clinical trial registry of India (CTRI) after ethic committee permission and before enrollment of first patient.

Informed Consent

Informed consent will be given freely after the subject has been informed of the nature, significance, implications and risks of the trial; and consent is evidenced in writing, dated and signed, or otherwise marked, by that person so as to indicate his/her consent, prior to the start of the study. The nature of the informed consent will comply with the principles that have their origin in the Declaration of Helsinki, the current requirements of GCP & ICMR guidelines.

Insurance and Indemnity

Participants will be insured against any injury caused by the study as per current legal requirements. All participants will be informed about the insurance. Medical care for all participants will be provided by the Principal Investigator and her team. In the event that the participant suffers an injury or dies and that is directly attributable to participation in the study, appropriate treatment will be provided and compensation will be provided by the CDRI/insurance company in compliance with rule 122-DAB-

compensation in case or injury or death during clinical trials" of the Drugs and Cosmetics Rules 1945 and its subsequent amendments.

12. Study Monitoring and Supervision:

Each clinical trial participant would be subjected to a detailed history taking, general and systemic examination and routine hematological, biochemical investigations and ECG recording before the drug administration. After drug administration each subject would be examined daily and his personal experiences and findings of clinical examination would be recorded on case sheets. A diary card will be provided to the participant to fill up the timing of experimental drug administration, breakfast and adverse events. All baseline laboratory investigations including ECG for both single dose and multiple dose study will be followed as per protocol mentioned above.

13. Investigational Product management:

Investigational Product(s): The drug Umifenvir will be manufactured in GMP facility and will be provided to investigator. All packaging and labelling as well as the production of study medication will be in compliance with GMP specifications, and any other or local applicable regulations.

Storage: Investigational product will be stored in dry and cool condition. The Sponsor and regulatory authorities will be permitted upon request to audit thee supplies, storage, dispensing procedures and records provided that the blind of the study is not compromised.

Accountability: In accordance with GCP, the Investigational Site will account for all supplies of drug Umifenovir and placebo. Details of Receipt, storage, assembly and return will be recorded.

14. Data analysis

For both the single and multiple dose studies, both within and between group comparisons will be done. The pre and post treatment biochemical investigations within

group will be done by paired students t-test. Between group (active drug versus placebo) will be analyzed by unpaired students t-test. The number of patients who experience adverse events or drop out will be expressed as percentage of the total. Between group analysis (active drug versus placebo) for drop outs and adverse events will be done the chi-square test or Fisher's test as appropriate. Multiple comparisons will be done using ANOVA followed by post hoc Dunnett's test. P valued less than 0.05 will be considered statistically significant.

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CONFIDENTIAL

CASE RECORD FORM

Protocol no. CDRI-CLINICAL-2/2020 Version 2 dated 4th June, 2020

The Universal Trial Number (UTN): U1111-1251-8421

Scientific Title of Study:

Phase 3, Randomized, Double-blind, Placebo control trial of Efficacy, Safety and Tolerability of Antiviral drug Umifenovir vs Standard care of therapy in non-severe COVID-19 patients.

Abbreviated Title: Efficacy and safety study of antiviral Umifenovir therapy in non-severe COVID-19 patients.

Subject's Initials:

Case No.:

Sponsor

COUNCIL OF SCIENTIFIC AND INDUSTRIAL RESEARCH-CENTRAL DRUG RESEARCH INSTITUTE

LUCKNOW – 226031

STUDY CONTACTS:

Investigators & Trial Center

Name:
King George Medical University, Lucknow Dr. Virendra Atam Dr. D. Himanshu Dr. Sudhir Verma
Era's Lucknow Medical College & Hospital, Lucknow Dr. Mohammad Moonis akbar Faridi Dr. Vaibav Shukla Dr. Jalees Fatima Dr. ZA khan Dr. Shirish Bhatnagar Dr. Hana Khan
RML Institute of Medical Sciences, Lucknow Dr. Vikram Singh Dr. A.K. Tripathi Dr. Hamant Kumar

DEMOGRAPHIC CHARACTERISTIC OF THE SUBJECT

1.Date of birth* (DD / MM / YY) Age in years

2. Date of Admission: 3. Date of Discharge
4.Patient ID (No.) 5. Occupation

Screening Visit Date/Time
Participant's initials :

Age Yrs

Height cms

Weight kg.

ASSESSMENT OF ELIGIBILITY FOR ENROLLMENT

• **Inclusion Criteria:**	**Yes/No**
○ Persons aged 18-75 years (inclusive), at the time of signing the Informed Consent Form (ICF), with symptoms of potential COVID-19 infection, including: fever, cough, shortness of breath, chills, muscle pain, new loss of taste or smell, vomiting or diarrhea and/or sore throat *WITH* Nasopharyngeal swab positivity in RT-PCR tests for SARS-Cov-2 antigens, shall be defined as symptomatic cases [WHO: Evaluating and Testing Persons for Coronavirus Disease 2019 (COVID-19) https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-criteria.html. Accessed on 30th April 2020]	
○ Asymptomatic persons aged 18-75 years (inclusive), at the time of signing the Informed Consent Form (ICF), *WITH* Nasopharyngeal swab positivity in RT-PCR tests for SARS-Cov-2 antigens, detected during screening of contacts or sentinel surveillance shall be defined as asymptomatic cases.	
○ Case categories according to severity (As per MOH, Govt of India guidlines):	
▪ Asymptomatic	
▪ Symptomatic	
• Mild	
• Moderate	
○ Chest imaging (CT as first option or digital X-ray if CT not possible)	
○ The interval between symptoms onset (or day of contact with a COVID-19 for asymptomatic patients detected during surveillance) and	

randomization is no more than 12 days; symptoms onset would primarily be based on pyrexia, or cough or other related symptoms for patients without experiencing pyrexia following onset.	
○ Eligible subjects of child-bearing age (male or female) must agree to take effective contraceptive measures (including hormonal contraception, barrier methods or abstinence) with his/her partner during the study period.	○
○ Not participating in any other interventional drug clinical studies before completion of the present study.	○
• **Exclusion Criteria:**	•
○ Severe COVID-19, as defined in (As per MOH, Govt of India guidlines):	○
○ Known allergy or hypersensitivity to Hesperidin	○
○ Possibility of the subject being transferred to a non-study hospital within 72h	○
○ Pregnant or lactating women	○
○ Severe liver disease: underlying liver cirrhosis or alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevated over 5 times the ULN;	○
○ Known severe renal impairment [creatinine clearance (CcCl) <30 mL/min] or having received continuous renal replacement therapy, hemodialysis or peritoneal dialysis	○
o Known disease or condition which may affect the study as decided by physician.	○

2. Systemic examination

a. General

b. Cardiovascular system (CVS)

c. Central nervous system (CNS)

d. Respiratory system (RS)

e. Perabdominal examination (PA)

Overall - Suitable for inclusion **Yes/No**

3. Lab Parameters

a. Haemoglobin gm%

b. Total leukocyte count /cc

c. Differential count L % N % E % B % M %

d. Platelet count /cc

e. Serum bilirubin

f. SGOT IU

g. SGPT IU

h. Alkaline phosphatase IU

i. Serum Creatinine gm%

j. Blood Urea gm%

k. Serum Electrolytes Na^+ K^+

l. Random Blood sugar gm%

m. Urine albumin gm%

n. Blood cells in urine Present/Absent

o. Pus cells in urine Present/Absent

p. Urine sugar Present/Absent

q. Stool for occult blood Positive/Negative

r. HIV status Positive/Negative

s. Report of chest X-ray Normal/Abnormal

t. 12 lead ECG findings Normal/Abnormal

4. Sitting blood pressure reading:

Pulse and respiration a) / mmHg

b) / mmHg

c) / mmHg

Rhythm: Regular/Irregular

Pulse Rate: / min

Respiratory Rate: / min

Volunteer eligible for inclusion	**Yes/No**

Time of Reporting at the Study Site:

Date and time of Clinical Examination:

Date and Time of Drug Administration:

S. No.	Date & Time
1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	

CLINICAL DATA SHEET

Please tick mark ( ) the appropriate alphabet.

TIME **Baseline** **Day 3** **Day 5, Day 7, Day 14** **Day 28**

---

1. **General**
   - A. Normal
   - B. Depressed
   - C. Anxious
   - D. Excited

   Conjunctive:
   - A. Normal
   - B. Congested
   - C. Lacrimation

   Pupils

   (a) Size
   - A. Normal
   - B. Dilated
   - C. Constricted

   (b) Reaction to light
   - A. Normal
   - B. Sluggish

   Temperature:

   Pulse- a. Rate

   b. Rhythm

   Blood pressure (mm Hg) Systolic/Diastolic

2. **Cardiovascular system**

   Complaints

   A. Palpitation / missing of beat

B. Vertigo

C. Any other

Examination

3. Respiratory system

Complaints:

A. Dyspnea

B. Respiratory distress

Auscultation

4. G.I. System.

Complaints:

A. Nausea

B. Vomiting

C. Diarrhea

D. Dryness of mouth

E. Hyperacidity

F. Loss of appetite

G. Flatulence

H. Pain

I. Salivation

Any other

5. Abdomen

Palpation;

a. Liver

b. Spleen

c. Glands

d. Gall bladder

e. Tenderness

f. Any other finding

2. **Genito - urinary system**

Complaints:

a. Frequency of micturition and amount
b. Haematuria
c. Difficulty in micturition
d. Libido
e. Retention of urine
f. Any other

3. **Breast complaints**
   a. Tenderness
   b. Any other
4. **Nervous System**

Complaints:

a. Tingling
b. Numbness
c. Motor weakness
d. Insomnia
e. Drowsiness
f. Visual disturbances
g. Headache
h. Giddiness
i. Anxiety
j. Irritability
k. Sweating
l. Confusion or euphoria
m. Flushing of face
n. Tinnitus
o. Misc, like indifference or apathy, muscular twitching or tremors
p. Any other Examination

A. Gait
B. Reflexes
C. Any other positive finding

5. **Skin rash or pruritus**
6. **WHO Ordinary Sclae for COVID-19**

7. **Any other tests done or finding observed**

Patient Status	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No limitation of activities	1
	Limitation of activities	2
Hospitalised Mild Disease	Hospitalised, no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalised Severe Disease	Non-invasive ventilation or high flow oxygen	5
	Intubation and mechanical ventialltion	6
	Ventillation +additional organ support- pressors, RRT, ECMO	7
Dead	Death	8

LABORATORY DATA SHEET

INVESTIGATION	Day 0	3,	7	10,	14	28

A. **HEMATOLOGY**

1. Hemoglobin (g %)
2. P.C.V. (%)
3. TLC (cum/mm)
4. DLC (%)
   Polymorphs
   Lymphocytes
   Monocytes
   Eosinophils
5. Corrected ESR (mm) fall 1 st Hr.
6. RBC Count (/ cu. mm.)
7. Platelet Count (/ cu.mm)
8. Platelet aggregation, if studied
9. Methhaemoglobin

B. **CLINICAL BIOCHEMISTRY**

I. Liver function tests

(i) S. Bilirubin (mg %)

(i) Free

(ii) Conjugated

(iii) Total

(ii) SGOT (I.U./L)

(i) SGPT (I.U./ L)

(ii) Alok. Phosphates (KA units/ U/ L)

(iii) Serum proteins (g %)

(i) Total serum proteins

(ii) Albumin (g%)

(iii) Globulin (g%)

II. Renal function tests:

i. S. Urea (mg%)
ii. S. Creatinine (mg%)

III. Lipid profile:

a. S. Cholesterol (mg%)
b. S. triglycerides (mg%)
c. HDL (mg%)

IV. Serum Electrolytes:

(i) Sodium (mEq./L)
(ii) Potassium (mEq./L)

V. Serum Glucose

Random (mg%)

C. Urine

(i) Reaction

(ii) Albumin

(iii) Sugar

(iv) Microscopic

(v) Any other finding

D. Stool

(i) Occult blood

(ii) Microscopic

E. E.C.G.

Normal/ Abnormal

(if abnormal give details)

F. Any other investigation

CLINICAL TRIAL MONITORING

Date	General Condition	Pulse Rate	Blood Pressure	ECG(To be done on Day 0, 7,14,30)	Remarks
0					
1					
2					
3					
44					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
30					

G: Adverse Event:

An adverse event is any undesired, noxious or pathological change in a patient or subject as indicated by signs, symptoms and / or laboratory changes that occurs in association with the use of trial medication whether or not considered drug-related. This definition includes intercurrent illness or injuries, exacerbation of pre-existing conditions and adverse events occurring as a result of drug withdrawal, abuse or overdose.

Serious adverse events:

All serious adverse events will be reported to the monitor in the form give in appendix within 24 hours by fax or by telephone.

Adverse events will be serious if any of the following apply:

- Events was fatal,
- Event was life-threatening,
- Hospitalization was prolonged,
- Patient was persistently or significantly disabled / incapacitated,
- Event was medically significant,
- Or required intervention to prevent one or other of the previous criteria.

Adverse Event Reporting Form

Code	Time and date of appearance of the symptom	Time and date of disappearance of the symptom	Action taken / treatment	Relation of event	Relationship to drug

Code	Relationship to Drug
1	None
2	Remote (unlikely) ≤ 5% chance of being related
3	Possible > 5% chance, but ≤ 50% chance of being related to study drug
4	Probable > 50% chance of being related to study

Informed Consent Document (ICD)

ICD no. CDRI-CLINICAL-ICD-2/2020 Version 1 dated 21st May, 2020
Protocol no. CDRI-CLINICAL-2/2020 Version 1 dated 21st May, 2020
The Universal Trial Number (UTN): U1111-1251-8421

Patient Information Sheet

Title: Efficacy and safety study of antiviral drug Umifenovir therapy in non-severe COVID-19 patients

You are invited to take part in this drug research study. The information in this form is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries, concerns or questions. You are being asked to participate in this study because you satisfy our eligibility criteria for the study.

1. What and why of the study?

Coronavirus disease 2019 also known as COVID-19 is a disease caused by corona virus SARS-CoV-2. It is a current health emergency for humankind that need cure in emergent mode. COVID-19 is causing deaths predominantly due to acute respiratory distress syndrome (ARDS) and lung failures that have been described in up to 20% of COVID-19 cases. The therapies currently available for COVID-19 all have limitations. Currently the drug Umifenovir has shown antiviaral activity in laboratory against SARS-CoV-2 which is a virus responsible for Coronavirus disease 2019. The drug Umifenovir also known as Arbidol is an antiviral agent useful for influenza illness. The drug is available in countries like Russia, China from years showing its excellent safety in Human beings. The Umfenovir drug has been tested in animals and humans in large number of experiments for other illness. Its clinical trials on corona virus disease are ongoing in other countries. So we wish to test efficacy and safety of drug Umifenovir in corona virus disease on Indian patients.

We have obtained permission from the Institute's Ethics Committee and Drug Controller General of India for conducting this study. You will be one of the ninety participants to take part in the study.

2. What will you be required to do during the study?

You will need to undergo complete check-up in our hospital, which will include clinical examination, blood tests, ECG, X ray/CT scan and urine test. If we are satisfied that you are physically and mentally fit, you will be allowed to participate.

There are two types of drugs that will be used in the study; they are:

1. Umifenovir 800mg two times a day for fourteen days along with standard care of therapy as per Ministry of Health, Govt of India guidelines.

2. Placebo (inactive medication which shall not have any therapeutic effect) with standard care of therapy including Hydroxychloroquine and Azithromycin

During the course of the study, you will need to take only one of the above and not all of them. However, which one of you will be given which of the above drugs will be depend only on chance. You will not know which drug is being given to you. This information will be with the person in-charge of the study and will be disclosed only in case of an emergency. The Umfenovir drug is an investigational drug for COVID-19 and there is a possibility of failure of investigational product to provide intended therapeutic effect.

You will need to give a blood (10 cc) and urine sample for checkup. The blood will be withdrawn at regular intervals throughout the study as per procedure. You will give approximately not more than 150ml of blood in total duration for testing purpose. You will be randomized to receive Umiferovin or placebo in addition to standard care of treatment. You have to take drug with one glass of water. You will be assessed clinically and by laboratory examination on days 1,3,5,7,14,21,28. You will be tested for nasopharyngeal swab testing on day 1,5,7,9,11,13,15,17,19,21,28. You may be advised to admit in hospital based on your health condition and treating doctor's decision. You will be treated as per hospital procedures by your physician. During the study period, you will be monitored so that any problems are detected. You will also be required to report to us if you feel anything abnormal. You will be required to take the drugs as instructed to you. You will also be required to follow all our instructions. If we

discover that you have violated our instructions, the compensation offered to you may be decreased depending on visit performed and you may be withdrawn from the study.

3. Possible risks to you

The drug has been found to be safe in extensive animal and human studies done all over world. This is the first time it will be given to corona virus disease indian patients; it is likely that it may cause some unexpected side effects to you (or to the embryo or foetus, if the you are female or may become pregnant), which are currently unforeseeable. However, you will be monitored continuously by experienced physicians and will be promptly treated if anything untoward happens. You will not have to pay for any treatment that you may have to undergo as a result of participating in the study. You or your representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect your willingness to continue participation, will be provided.

4. Possible benefits to you

You are not expected to get any benefit from participating in this research study. However, you will get the benefit of free medical check-up.

5. Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

If the drug is ultimately successfully marketed, the company responsible for its development will also be benefited.

6. The alternatives you have

The only alternative you have got is not to participate in this study. Your treatment at hospital will not be affected by your decision to not to participate in study.

7. Cost to the participant

You will not be required to pay for the medications, investigations and stay in the hospital. Compensation for inconvenience, visits, hospital stay, blood samples: You will be paid a nominal compensation for your participation. However, if you leave the study in between and without any reason, you will not be entitled to full payment upon your level of participation.

8. Compensation for participation in this study

Since you will need to spend time and effort to participate in this study, and give some blood samples, you will be compensated for all this inconvenience. You will also be paid for your traveling expenses.

This compensation depends on the level of your participation and the number of blood samples you are asked to give. The travelling allowance may be given for participating in study as per government travelling rules. The total travelling amount will not exceed Rs. 1000. Compensation for volunteers taking part in the trial can be based on the following revised criteria

- Per Blood Collection = Rs. 100/-
- Per Day of Admission = Rs. 2,000/-
- Per Screening Admission = Rs. 500/
- However, if you are found to have concealed some information or do not follow our instructions, we may deduct from your compensation amount depending on your level of participation what is due to you.

In case of any adverse event occurring due to the study medications or death, King George Medical Univesity, Lucknow will provide complete medical care. The volunteer will be insured. The cost of medical care along with compensation for the injury or death will be borne by sponsor.

09. What should you do in case of injury or a medical problem during this research study?

Your safety is the prime concern of the research. Even though you may have risk of any injury which are currently unforeseeable. If you are injured or have a medical problem as a result of being in this study, you should contact one of the people listed at the end of the consent form.

(a) In case of an injury occurring to you during the clinical trial, free medical management shall be given as long as required or till such time it is established that the injury is not related to the clinical trial, whichever is earlier.

(b) In the event of a trial related injury or death, the sponsor or his representative or the investigator or centre, as the case may be, in accordance with the rule 39, as the case may be, shall provide financial compensation for the injury or death. You will be insured for your health for this study. You are free to obtain relief as per legal procedures.

10. Confidentiality of the information obtained from you?

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, your medical history. By signing this document you will be allowing the research team investigators, other study personnel, sponsors, institutional review board and with any person or agency required by law like Drug Controller General of India. Your information may be kept and used indefinitely by the sponsor.

The identity of the drug that you or other participants have received will not be revealed to you. You may know it when the research is completed.

The results of clinical tests and therapy performed as part of this research may be included in your medical record. The information from this study if published in scientific journals presented at scientific meetings will not reveal your identity.

12. How will your decision to not participate in the study affect you?

Your decision to not participate in this research study will not affect your your relationship with the investigator or the King George medical University, Lucknow.

13. Can you decide to stop participating in the study once you start?

You can stop being in this research study i.e. you have the right to withdraw at any time during the course of the study. Your decision to withdraw will not affect your

relationship with the investigator or the institute (King George University, Lucknow). It will not involve any penalty to you.

However, it is advisable that you talk to the research team prior to stopping the treatment. You may be advised about how best to stop the treatment safely. If you withdraw, you may be asked to undergo some additional tests to which you may/may not agree. Though advisable that you give the investigators the reason for withdrawing, it is not mandatory.

14. Can the investigator take you off the study?

You may be taken off the study if you don't follow instructions of the investigators or the research team. The investigator may also stop your treatment midway if it is in your best interest.

15. Right to new information

If the research team gets any new information during this research study that may affect your decision to continue participating in the study, or may raise some doubts, you will be informed accordingly by the clinical investigator.

16. Contact persons (in case of adverse event)

Name:
King George Medical University, Lucknow 1. Dr. Virendra Atam M.D., Prof. & Head, Department Medicine, King George Medical University, Lucknow (Principal Investigator - Clinical Trial Site) Email: v_atam@yahoo.com Mobile 99839806676, Phone: 0522 225 8880 Dr. D. Himanshu Dr. Sudhir Verma

Era's Lucknow Medical College & Hospital, Lucknow Dr. Mohammad Moonis akbar Faridi Principal & Chief Medical Superintendent, Era's Medical College, Lucknow Email: drmmafaridi@gmail.com Mobile: 8800696442 Dr. Vaibav Shukla Dr. Zalees Fatima Dr. ZA khan Dr. Shirish Bhatnagar Dr. Hana Khan
RML Institute of Medical Sciences, Lucknow Dr. Vikram Singh, Department of General Medicine, Dr. Ram Manohar Lohia Institute and Medical Sciences Lucknow. Mobile 9680005076 Dr. A.K. Tripathi Dr. Hamant Kumar

INFORMED CONSENT FORM

Study Title: Efficacy and safety study of antiviral Umifenovir therapy in non-severe COVID-19 patients

Study number: CDRI-CLINICAL2/2020

Subject's Initials: _____ Subject's Name: _____

Date of Birth / Age : _____ (____)
Address of the subject
Qualification
Occupation: Student/Self-employed/ Service/ Housewife/ Others (Please tick as appropriate)
Annual income of the subject:

Name of the address of the nominee (s) and his relation to the subject_____

(for the purpose of the compensation in case of the trial related deaths. Please initial box

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Sponsor of the clinical trial, others working on the Sponsor's behalf, the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s). [ ]

(v) I agree to take part in the above study. [ ]

(Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Signatory's Name: _____Date____/_____/_____

Signature of the Investigator: _____Date____/____/_____

Study Investigator's Name:_____ Date ____/____/_____

Signature of the Witness:_____ Date ____/____/_____

Name of the Witness:_____

"(Copy of the Patient Information Sheet and duly filled Informed Consent Form shall be handed over to the subject or his/her attendant)."

सूचित सहमति पत्र

सूचित सहमति पत्र सं. सीडीआरआई -क्लीनिकल-सूसप२/२०२० संस्करण २ दिनांक ४ जून २०२०
प्रोटोकॉल सं. सीडीआरआई –क्लीनिकल-२/२०२० संस्करण २ दिनांक ४ जून २०२०
विश्वव्यापी **परीक्षण संख्या : युटीन ११११ -१२५१ -८४२१**

रोगी सूचना पत्र

अध्ययन का नाम: गैर-गंभीर कोविड-१९ रोगियों में एंटीवायरल दवा उमिफेनोविर थेरेपी की प्रभावकारिता और सुरक्षा का अध्ययन.

आपको इस दवाई के अभ्यास में शामिल होने के लिए आमंत्रित किया जा रहा है. इस पत्र में दी हुई जानकारी से आपको यह तय करने में सहायता मिलेगी की आपको इस अभ्यास में शामिल होना है की नहीं।आपके मन में कोई भी प्रश्न या चिंता हो तो आप बेझिझक पूछ सकते है. आपको इस दवाई के अभ्यास में शामिल होने के लिए आमंत्रित किया जा रहा है, क्योंकि आप अध्ययन के लिए हमारी पात्रता मानदंडों को संतुष्ट करते हैं।

१) यह अभ्यास क्या है और क्यों किया जा रहा हैः

कोरोना वायरस SARS-CoV-2 के कारण उत्पन्न कोविड–19 बीमारी, मानवजाति के लिए इस समय एक स्वास्थ्य आपातकाल समस्या है। जिसे आकस्मिक ढंग से दूर करने की जरूरत है। कोविड–19 के गम्भीर मामलों में 20% तक मामले में कोविड–19 के तीव्र श्वसन संकट सिन्ड्रोम और फेफड़ों की विफलता के कारण मृत्यु हो रही है। वर्तमान में कोविड–19 बीमारी में उपलब्ध चिकित्सा की सभी सीमाएँ हैं। वर्तमान में दवा उमिफेनोविर ने SARS-CoV-2 के खिलाफ प्रयोगशाला में एंटीवायरल गतिविधि दिखाई है। SARS-CoV-2 जो कि कोरोनावायरस बीमारी 2019 के लिए जिम्मेदार एक वायरस है। दवा उमिफेनोविर को आर्बिडोल के रूप में भी जाना जाता है, यह एक एंटीवायरल एजेंट है जो इन्फ्लूएंजा बीमारी के लिए उपयोगी है। यह दवा रूस, चीन जैसे देशों में वर्षों से उपलब्ध है जिसकी मानवों में अपनी उत्कृष्ट सुरक्षा साबित हो चुकी है। दवा उमिफेनोविर का अन्य बीमारी के लिए बड़ी संख्या में प्रयोगों में जानवरों और मनुष्यों में परीक्षण किया गया है। कोरोना वायरस रोग पर इसके नैदानिक परीक्षण अन्य देशों में चल रहे हैं। इसलिए हम भारतीय रोगियों पर कोरोना वायरस रोग में दवा उमिफेनोविर का प्रभावकारिता और सुरक्षा का परीक्षण करना चाहते हैं।

इस अभ्यास के लिए हमने हमारे संस्थान की नैतिकता समिति और भारतीय औषध महासंचालक से अनुमति प्राप्त की है. अध्ययन में भाग लेने के लिए आप नब्बे स्वयंसेवकों में से एक होंगे।

२) अध्ययन के दौरान आपको क्या करना होगा?

आपको हमारे अस्पताल में पूरी जांच कराने की आवश्यकता होगी, जिसमें शामिल होगा नैदानिक शारीरिक परीक्षा, रक्त परीक्षण, ईसीजी, एक्स रे / सीटी स्कैन और मूत्र परीक्षण। अगर हम संतुष्ट हैं कि आप शारीरिक और मानसिक रूप से फिट हैं तभी आपको अभ्यास में भाग लेने की अनुमति होगी

अध्ययन में दो प्रकार की दवाओं का उपयोग किया जाएगा; वो हैं:

1. उमिफेनोविर दवाई ८०० मिलीग्राम दिन में दो बार चौदह दिनों के लिए, चिकित्सा की मानक देखभाल के साथ। स्वास्थ्य और परिवार कल्याण मंत्रालय के दिशानिर्देश अनुसार चिकित्सा की मानक देखभाल किया जाएगा ।
2. प्लेसबो (निष्क्रिय दवा जिसका कोई उपचारात्मक प्रभाव नहीं होगा), चिकित्सा की मानक देखभाल के साथ। स्वास्थ्य और परिवार कल्याण मंत्रालय के दिशानिर्देश अनुसार चिकित्सा की मानक देखभाल किया जाएगा ।

अध्ययन के दौरान, आपको केवल उमिफेनोविर अथवा प्लेसबो कोई एक लेने की आवश्यकता होगी। यह मौका पर ही निर्भर करता है की कौन सी दवा आप को दी जा रही है । यह जानकारी अध्ययन के प्रभारी व्यक्ति के साथ होगी और आपातकाल के मामले में ही इसका खुलासा किया जाएगा। कोविड–19 बीमारी के लिए उमिफेनोविर एक अनुसंधानात्मक जांच दवा है जिसकी प्रभाव विफलता की संभावना है।

आपको चेकअप के लिए रक्त (10 cc) और मूत्र का नमूना देना होगा। प्रक्रिया के अनुसार पूरे अध्ययन में नियमित अंतराल पर रक्त निकाला जाएगा। आप परीक्षण उद्देश्य के लिए कुल अवधि में लगभग 150 मिलीलीटर से अधिक रक्त नहीं देंगे। आपको उपचार की मानक देखभाल के अलावा उमिफ़ोरोविन या प्लेसबो प्राप्त करने के लिए क्रम रहित तरीको से शामिल किया जाएगा। आपको एक गिलास पानी के साथ दवा लेनी होगी। आपका १, ३,५, ७,१४,२१,२८ दिनों में शारीरिक परीक्षा और प्रयोगशाला परीक्षण द्वारा मूल्यांकन किया

जायेगा। आपका १,५,७,९,११,१३,१५,१७,१९,२१,२८ दिन में नाक और गले का स्वाब परीक्षण का परीक्षण किया जायेगा। आपको अपने स्वास्थ्य की स्थिति और डॉक्टरों के निर्णय के आधार पर अस्पताल में भर्ती करने की सलाह दी जा सकती है। आपका अपने चिकित्सक द्वारा अस्पताल की प्रक्रिया के अनुसार इलाज किया जायेगा। अध्ययन अवधि के दौरान, आप पर नजर रखी जाएगी ताकि कोई भी समस्या हो तो हमें पता चले । अगर आप भी कुछ असामान्य महसूस करते हैं तो हमें बताये।

आपको निर्देश के अनुसार दवा लेने की आवश्यकता होगी। आपको हमारे सभी निर्देशों का पालन करना भी आवश्यक होगा। अगर हमें पता चलता है कि आपने हमारे निर्देशों का उल्लंघन किया है, तो आपके द्वारा दिए गए मुआवजे को अध्ययन में भागीदारी का स्तर आधार पर कम किया जा सकता है और आपको अध्ययन से हटा दिया जा सकता है। हालांकि, अध्ययन अवधि के दौरान अध्ययन से संबंधित चोटों के लाभ तभी भी प्राप्त कर सकते है.

३) आपके लिए संभव जोखिम

इस दवा को सी डी आर आई में किये गए व्यापक पशु अध्ययनों में सुरक्षित पाया गया है. चुकी यह पहली बार कोविड-१९ मनुष्य को दी जाएगी, यह संभावना है कि इस दवाई से कुछ अप्रत्याशित दुष्प्रभाव हो सकते है. यदि आप गर्भवती महिला हैं या हो सकती हैं तो दवाई से कुछ अप्रत्याशित दुष्प्रभाव आपको या भ्रूण को हो सकते है. इसलिए गर्भवती महिलाओं को अध्ययन की अनुमति नहीं है. हालांकि, अनुभवी चिकित्सकों द्वारा आपकी लगातार निगरानी की जाएगी और अगर कुछ भी अयोग्य होता है तो तत्काल इलाज भी किये जायेंगे. आपको किसी भी ऐसे उपचार के लिए भुगतान नहीं करना होगा जिसे आपको भाग लेने के परिणामस्वरूप गुज़रना पड़ सकता है.

आप किसी भी समय अध्ययन से बाहर निकलने के लिए स्वतंत्र हैं। पर उससे पहले अन्वेषक को पूर्व सूचना देनी चाहिए या देना उचित होगा ।

४) आपके लिए संभव लाभ

इस शोध अध्ययन में भाग लेने से आपको कोई लाभ प्राप्त होने की उम्मीद नहीं है।

हालांकि, आपको निःशुल्क चिकित्सा जांच का लाभ मिलेगा.

५) अन्य लोगों को संभावित लाभ

शोध के परिणाम के समाज को लाभ प्रदान कर सकते हैं जैसे की इससे चिकित्सीय लाभ की उन्नति हो सकती है या फिर भविष्य के रोगियों को उपचार देने में इस चिकित्सा ज्ञान का फायदा हो सकता है। यदि दवा अंततः सफलतापूर्वक विपणन (बाजार में बेचीं) की जाती है, तो उसके लिए जिम्मेदार कंपनी विकास भी होगा।

६) आपके पास उपलब्ध विकल्प

इस अध्ययन में भाग नहीं लेना ही आपके पास एकमात्र उपलब्ध विकल्प है.

७) प्रतिभागी को लागत

आपको दवाओं, जांच के लिए, अस्पताल रहने के लिए कोई भुगतान करना नहीं होगा। आपको होने वाली असुविधा, यात्रा, अस्पताल के रहने, रक्त के नमूने, आपकी भागीदारी के लिए जैसे दिया गया है वैसे मुआवजे का भुगतान किया जाएगा.लेकिन, अगर जांचकर्ताओं का फैसला है की आपको अध्ययन से बाहर करना है तो, आपको जो कुछ भी भुगतान मिलेगा वो आपकी भागीदारी का स्तर पर निर्भर करेगा।

८) इस अध्ययन में भागीदारी के लिए मुआवजा

चूंकि आपको इस अध्ययन में भाग लेने के लिए समय और प्रयास खर्च करने की और कुछ रक्त के नमूने देने भी आवश्यकता होगी,आपको इस असुविधा के लिए मुआवजा दिया जाएगा। आपके यात्रा के खर्चों के लिए भी भुगतान किया जाएगा। यह मुआवज़ा आपकी भागीदारी के स्तर और रक्त के नमूनों की संख्या पर निर्भर करता है.

अध्ययन में भाग लेने वाले स्वयंसेवकों के लिए मुआवजा लगभग रु. 5,400 और निम्नलिखित संशोधित मानदंडों के आधार पर होगा

- प्रति रक्त संग्रह = रु। १०० / -
- प्रवेश के प्रति दिन = रु। २०००/ -
- प्रति स्क्रीनिंग प्रवेश = रु। ५०० /-

अध्ययन दवाओं के कारण होने वाली किसी प्रतिकूल घटना के मामले में, आप को हमारे संस्थान में नि: शुल्क उपचार प्रदान किया जायेगा और इसमें शामिल किसी भी लागत का प्रायोजक द्वारा वहन किया जाएगा।

९) यह शोध अध्ययन कोई चोट या एक चिकित्सा समस्या के मामले में आपको क्या करना चाहिए ?

आपकी सुरक्षा अनुसंधान की मुख्य उद्देश्य है. यदि इस अध्ययन में होने के परिणामस्वरूप आप घायल हो गए या आपको कोई समस्या हो तो आपको उन लोगों में से एक से संपर्क करना चाहिए जो सहमति फार्म के अंत में सूचीबद्ध हैं । या उनके वहां अस्पताल में जा सकते है.

(a) चिकित्सीयपरीक्षण प्रतिभागी को होनेवाली किसी भी परीक्षणसंबंधी चोट की स्थिति में, प्रतिभागी के लिए जब तक आवश्यक हो, तब तक नि: शुल्क चिकित्सा प्रबंधन दिया जाएगा या यह स्थापित किया जानेतक कि चोट नैदानिक परीक्षण से संबंधित नहीं है, जो भी पहले हो।

(b) चिकित्सीय परीक्षण से संबंधित किसी चोट या मृत्यु की स्थिति में, मे. प्रायोजक, या उनके प्रतिनिधि या अन्वेषक या केंद्र, जैसा भी मामला हो राष्ट्रीय नियामक प्राधिकरण की लागू दिशानिर्देशों या नियम ३९ अनुसार वित्तीय मुआवजा प्रदान करेगा. आप इस अध्ययन के लिए अपने स्वास्थ्य के लिए बीमित होंगे। इस के अलावा आप अपने कानूनी अधिकारों के हकदार होंगे।

११) आपके द्वारा प्राप्त की गई जानकारी की गोपनीयता -

आपको अपनी चिकित्सा की जानकारी (व्यक्तिगत विवरण, शारीरिक परीक्षाओं के परिणाम, जांच, आपकी चिकित्सा का इतिहास) के बारे में गोपनीयता का अधिकार है.

इस दस्तावेज़ पर हस्ताक्षर करके आप अनुसंधान दल को अनुमति दे देंगे की यह जानकारी जांचकर्ताओं, अन्य अध्ययन कर्मियों, प्रायोजकों, संस्थागत समीक्षा बोर्ड और भारत के ड्रग कंट्रोलर जनरल की तरह विधि द्वारा आवश्यक व्यक्ति या एजेंसी को जरुरत पड़ने पर यह जानकारी मुहैया करेंगे। प्रायोजक द्वारा तुम्हारी जानकारी को अनिश्चित काल तक रखा जा सकता है. इस शोध के भाग के रूप में किए गए नैदानिक परीक्षणों और चिकित्सा के परिणाम आपके मेडिकल रिकॉर्ड में शामिल किये जा सकते है. यदि इस अध्ययन से मिली जानकारी वैज्ञानिक बैठकों में प्रस्तुत की जाती है या फिर वैज्ञानिक पत्रिकाओं में प्रकाशित होती है तो उसमे आपकी पहचान प्रकट नहीं होगी।

१२) अध्ययन में भाग न लेने के लिए आपका फैसला आपको किस प्रकार प्रभावित करेगा?

इस शोध अध्ययन में भाग न लेने का आपका निर्णय आपके जांचकर्ता या किंग जॉर्ज मेडिकल विश्वविद्यालय के साथ अपने संबंधो को प्रभावित नहीं करेगा.

१३) क्या आप शुरू करने के बाद अध्ययन में भाग लेने से मना कर सकते हैं?

आप इस शोध अध्ययन में शामिल होने से मना कर सकते हैं. इस शोध अध्ययन में भाग न लेने का आपका निर्णय आपके जांचकर्ता या किंग जॉर्ज मेडिकल विश्वविद्यालय अस्पताल के साथ अपने संबंधो को प्रभावित नहीं करेगा. हालांकि, आप उपचार रोकने से पहले अनुसंधान टीम से बात करें क्यूंकि आपको यह सलाह दी जा सकती है कि उपचार को सुरक्षित रूप से कैसे रोका जाये।

सहमति वापस लेने के लिए, आपको कुछ अतिरिक्त परीक्षणों से गुजरना कहा जा सकता है, जिसके लिए सहमत हो ऐसे जरुरी नहीं। हालांकि यह अनिवार्य नहीं है पर आपको सलाह दी जाती है कि आप जांचकर्ताओं को सहमति वापस लेने का कारण बताये।

१४) क्या अन्वेषक आपको इस अभ्यास से बाहर कर सकता है?

अगर आप अनुसन्धान दल के दिए हुए निर्देशों का पालन नहीं करते है तो आपको अभ्यास से बाहर किया जा सकता है.अगर अन्वेषक को लगता है की आपका इस अभ्यास में न होना ही आपको हित में है तभी भी आपको इस बाहर किया जा सकता है.

१५)नई जानकारी का अधिकार

आप को किसी भी नई जानकारी के बारे में अन्वेषक द्वारा बताया जाएगा जो इस अध्ययन में आप को शामिल होने की अनुमति देने का अपका फैसला बदल सकता है.

१६) अधिक जानकारी के लिए संपर्क करें:

इस अध्ययन की जानकारी पढ़ने के लिए आपने जो समय दिया उसके लिए धन्यवाद

इससे पहले कि आप इस दस्तावेज़ पर हस्ताक्षर करें, आप को जो भी समाज में नहीं आया उस बारेमे सवाल पूछ सकते है. अध्ययन स्टाफ अध्ययन के पहले, दौरान और बाद के सवालों के जवाब जरूर देगा।

यदि आपके इस अध्ययन के बारे में, या यह कैसे चलाया जा रहा है, दवा के दुष्प्रभाव या अनुसंधान से संबंधित बीमारी या चोट के बारेमे प्रश्न हैं तो आप नीचे दिए गए अध्ययन डॉक्टर से संपर्क कर सकते हैं।

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डॉ। शिरीष भटनागर
डॉ। हाना खान

आरएमएल इंस्टीट्यूट ऑफ मेडिकल साइंसेज, लखनऊ
डॉ। विक्रम सिंह, सामान्य चिकित्सा विभाग, डॉ। राम मनोहर लोहिया संस्थान और चिकित्सा विज्ञान लखनऊ।
मोबाइल 9680005076
डॉ। ए.के. त्रिपाठी
डॉ। हामंत कुमार

यदि आपके प्रश्नों का जवाब आपको संतोषजनक रूप से मिला है तभी इस पर हस्ताक्षर करें.

सूचित सहमति फार्म

संक्षिप्त शीर्षक अध्ययन का नाम: गैर-गंभीर कोविड-१९ रोगियों में एंटीवायरल दवा उमिफेनोविर थेरेपी की प्रभावकारिता और सुरक्षा का अध्ययन.

प्रोटोकॉल संख्या: सीडीआरआई -क्लीनिकल-२/२०२० संस्करण 1 दिनांक 11 मई 2020

प्रतिभागी लघुहस्ताक्षर: _____ **प्रतिभागी का नाम**: _____

प्रतिभागी आईडी: _____ **जन्मतिथि:** _____

प्रतिभागी का विवरण:

पता:

_____

_____

शैक्षणिक योग्यता: _____

व्यवसाय: छात्र / निजी व्यवसाय / नौकरी / गृहिणी / अन्य (कृपया उपयुक्त के रूप में चिह्नित करें)

वार्षिक आय: _____

मनोनीत व्यक्ति (नॉमिनी) नाम औरउम्मीदवार का पता -परीक्षण संबंधी मृत्यु के मामले में:

_____

कृपया केवल बॉक्समें लघुहस्ताक्षरकरें

(I) मैंने इस अध्ययन के बारे में अधिसूचित संविदा दस्तावेज में दी जानकारी को पढ़ा है [ ]

(II) मुझे इस अध्ययन के प्रकृति, उद्देश्य, अवधि और परीक्षण के निकट भविष्य के प्रभाव और जोखिम का विवरण प्राप्त हुआ है और मुझे क्या करना होगा इसकी जानकारी प्राप्त हुई है । मेरे सारे सवालों का उत्तर संतोषजनक रूप से किया गया है। [ ]

(III) मैं समझता हूं कि परीक्षण में मेरी भागीदारी स्वैच्छिक है और मैं किसी भी समय जुर्माना या लाभ के नुकसान के बिना किसी भी समय भाग लेने से इनकार कर सकता हूं या फिर परीक्षण से सम्मति वापस ले सकता हूं. [ ]

(IV) मैं आगे यह समझता हूं कि जो जानकारी उस अध्ययन के दौरान उपलब्ध हो सकती है जो भाग लेने की मेरी इच्छा को प्रभावित कर सकती है, मुझे सूचित किया जाएगा। [ ]

(V) संस्थागत नैतिकता समिति के अधिकारि अध्ययन में एकत्रित जानकारी सत्यापित करने के लिए मेरे मेडिकल रिकॉर्ड की जांच सकते हैं। इस दस्तावेज़ पर हस्ताक्षर करके, मैं अपने अभिलेखों की समीक्षा के लिए अनुमति देता हूं। [ ]

(VI) मैं समझता हूं कि मेरी पहचान किसी भी रिपोर्ट या प्रकाशन में प्रकट नहीं होगी। [ ]

(VII) मैं उपरोक्त अध्ययन में भाग लेने के लिए सहमत हूं। [ ]

_____

प्रतिभागी से संबंध: _____

_____	_____	_____
अध्ययन में भाग लेने वाले व्यक्ति का नाम	**अध्ययन के प्रतिभागियों हस्ताक्षर / अंगूठे का निशान**	**तारीख**
_____	_____	_____
कानूनी प्रतिनिधि का नाम	**कानूनी प्रतिनिधि के हस्ताक्षर /अंगूठे का निशान_** _____ **अध्ययन में शामिल व्यक्ति के साथ रिश्ता**	**तारीख**

निष्पक्ष गवाह का नाम	**निष्पक्ष गवाह के हस्ताक्षर**	**तारीख**
सहमति लेने वाले व्यक्ति का नाम	**सहमति लेने वाले व्यक्ति के हस्ताक्षर**	**तारीख**

"(रोगी सूचना पत्र की प्रतिलिपि और विधिवत भरे हुए सूचित सहमति फॉर्म को अध्ययन के प्रतिभागियों या उसके परिचर को सौंप दिया जाएगा।)

CURICUULAM VITAE OF INVESTIGATORS

Dr. Tapas Kundu, Director CSIR-CDRI

Principal Investigator (Last, First, Middle):

BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. DO NOT EXCEED FIVE PAGES.

NAME: Tapas K Kundu

POSITION TITLE: Professor and Director, CSIR-CDRI

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include post-doctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Bidhan Chandra Agricultural University, Mohanpur, India	B.Sc	06/1986	Biochemistry
University of Agricultural Sciences, GKVK, Bengaluru, India	M.Sc	06/1989	Biochemistry
Indian Institute of Sciences, Bengaluru, India	Ph.D.	09/1995	Molecular Biology
National Institute of Genetics, Mishima, Japan	RA	09/1996	Molecular Genetics
The Rockefeller University, New York City, NY, USA	Post-Doctoral Fellow	10/1999	Biochemistry and Molecular Biology

A. Personal Statement

My research experience began with a Master's degree in Biochemistry from University of Agricultural Sciences, Bangalore in 1989, winning a gold medal for standing first in the master's degree examination. I then joined the lab of Prof MRS Rao at Indian Institute of Science in 1990 and secured a PhD in 1995 for the thesis, 'Zinc-Metalloprotein Nature of Rat Spermatidal Protein TP2 and its Interactions with DNA".

During a short stint as a visiting foreign research associate in the National Institute of Genetics, Mishima, Japan, I contributed to the field of prokaryotic transcription. As a Post-Doctoral Fellowship at the Rockefeller University, USA (1996-99), the focus of my work shifted to epigenetic regulation of eukaryotic transcription, in which I continue making seminal discoveries till date.

I joined JNCAS, Bengaluru, India as a Faculty fellow in 1999 and established the Transcription and Disease Laboratory in the year 2000 at the Molecular Biology and Genetics Unit. The major focus of the laboratory is to understand the mechanism of chromatin dynamics which is responsible for the regulation of gene expression, with special emphasis on transcription. One of the important themes of the laboratory is the elucidation of the epigenetic language that regulates transcriptional outcomes in physiological and pathophysiological states such as cancer, AIDS, diabetes and neurodegenerative diseases. My group is also actively involved in the identification of small molecule modulators of chromatin modifying enzymes from natural sources through chemical biology approaches. Since these molecules have tremendous potential to be used in epigenetic therapy, strategies for delivery of these synthesized and derivatized molecules in cell lines, stem cells and animal models are being investigated using different nanoparticles conjugated with the small molecule modulators.

I joined CSIR-CDRI in August 2018 as Director, wherein, I initiated multipronged activities to create conducive environment for fundamental research driven biomedical innovation in the disease areas of National importance. Some important accomplishments include: (1) Fast tracking the development of promising leads and candidate drugs - Filed IND for Antithrombotic lead and getting ready for filing IND for Fracture Healing lead; (2) Setting-up of academic collaboration with IITs of Guwahati, Bombay, Indore, Kanpur, Madras and also other private institution of relevance; (3) Collaborating with CIPLA, a leading global pharma industry for development of Levo-ormeloxifene for various indication like Contraceptive, anticancer etc.

Key Personnel Biographical Sketch

Principal Investigator (Last, First, Middle):

B. Positions and Honors

Position	Institution	Period
Visiting Foreign Research Associate	Department of Molecular Genetics, National Institute of Genetics, Mishima, Japan	1995-1996
Post-Doctoral Fellow	Laboratory of Biochemistry and Molecular Biology The Rockefeller University, New-York, USA.	1996-1999
Faculty Fellow (Assistant Professor)	Transcription & Disease Laboratory, Molecular Biology and Genetics Unit, Jawaharlal Nehru Centre for Advanced Scientific Research (JNCASR), Bengaluru, India	1999-2004
Associate Professor	Transcription & Disease Laboratory, Molecular Biology and Genetics Unit, JNCASR, Bengaluru, India	2004-2009
Professor	Transcription & Disease Laboratory, Molecular Biology and Genetics Unit, JNCASR, Bengaluru, India	2009-Present (on lien)
Director	CSIR-Central Drug Research Institute, Lucknow, India	2018-Present

Academic and Professional Honours

1) 1990, Gold Medal for securing first position in M.Sc., G.K.V.K, Bangalore, India
2) 1995, GIRI MEMORIAL AWARD for best thesis in Biochemistry, IISc. India.
3) 1996, COE Visiting Scientist fellowship from MONBUSHO, Government of Japan
4) 2001, International Union against Cancer, Fellowship, Switzerland: Based on project proposal, the fellowship was used to perform collaborative research work at Cancer Research, London. UK.
5) 2001, Human Frontier Science Program Organization, Fellowship, France: Based on project proposal, to perform collaborative research.
6) 2005, International Union against Cancer, Fellowship, Switzerland: Based on project proposal, the fellowship was used to perform collaborative research work at Kyoto University, Japan.
7) **National Bioscience award** for career development, DBT, Govt. of India, 2004-05: As per the citation, "National Bioscience Award for career development was conferred on outstanding contribution towards understanding the regulation of eukaryotic (human) transcription from chromatin template"
8) **Shanti Swarup Bhatnagar prize** in **2005** from CSIR, Govt. of India. As per the citation, "The Shanti Swarup Bhatnagar Prize for the year 2005 in Biological Sciences has been awarded to Dr. Tapas Kumar Kundu of the JNCASR, for outstanding research in the area of chromatin transcription. He has identified PC4 as a functional component of chromatin and as a unique activator of p53. He has established the role of acetylation in chromatin transcription and histone chaperone activity, besides using this process for identifying new drug candidates"
9) India-France ARCUS-INDIA grant for collaborative research Fellowship (2005-08).
10) **National Academy of Science, India- Reliance Industries Platinum Jubilee Award, 2008**, has been awarded for the outstanding contribution in the area of regulation of human gene expression (transcription) and its link to disease and therapeutics
11) **Tohoku Medical Society, Tohoku University, Japan, Lecture Medal,** 2010.
12) **Sir J C Bose National Fellowship,** Department of Science and Technology, Govt. of India, 2010.
13) **GD Birla award for Scientific Research for 2011.** Citation: "Kundu's contributions are outstanding in the area of regulation of human gene expression (transcription) and its link to disease and therapeutics which is also being used to design new generation cancer diagnostics, as well as therapeutics for cancer, AIDS and diabetes. Kundu has also identified PC4 as a functional component of chromatin and as a unique activator of p53.
14) **Ranbaxy Research Award** for the year 2011 in the field of "Medical Sciences – Basic Research. Citation:" His research work has made significant contribution in the area of epigenetic and gene regulation with special emphasis on disease. His work for the first time established the causal relationship of histone and non-histone protein hyperacetylation in the manifestation of oral cancer and Bovine mastitis. He has also developed a nano device to induce acetylation of histones in the mice brain which could be highly useful for the treatment of neurodegenerative diseases."

Key Personnel Biographical Sketch

Principal Investigator (Last, First, Middle):

15) First place in the **India Innovation Award 2012 given by Merck Millipore,** awarded to Prof Tapas K Kundu and team, based on their US patent on Site -specific HMTase inhibitors. Citation: Tapas K Kundu, and three of his previous group members, Selvi Ruthrotha Bharatha Vikru (PhD student), Hari Kishore Annavarapu (R&D assistant), Mantelingu Kempegowda (Research Associate) of Transcription and Disease Laboratory, MBGU, JNCASR, have received the first prize of India Innovation Award given by Merck Millipore company on 29th October 2012, based on one of their US patents, entitled, "Site-Specific Inhibitors of Histone Methyltransferase (Hmtase) and Process of Preparation Thereof"
16) **Silver Jubilee Professorship of JNCASR for the academic year 2015-2016**, Awarded by the C.N.R. Rao Education Foundation Silver Jubilee Professorship of JNCASR for the academic year 2015-2016, Awarded by the C.N.R. Rao Education Foundation
17) **Dr. Nitya Anand endowment lecture award** by Indian National Science Academy, 2015.
18) **G.P. Chatterjee Memorial Award for 2015-2016, awarded by the Indian Science Congress** Association, Ministry of Science and Technology, Govt. of India. Presented at the 103rd Indian Science Congress, January 2016.
19) **Degree of D.Sc. Honoris Causa** from **Uttar Banga Krishi Viswavidyalay, Govt. of West Bengal, India,** in the year 2018.
20) **Shri Om Prakash Bhasin Award 2019** in the field of **Health & Medical Sciences.**

Membership on Government public advisory committee

1) Member, Drugs Technical Advisory Board, CDSCO, DGHS, Ministry of Health & Family Welfare, India
2) Member, Technical Expert Committee on Nanobiotechnology, DBT, India
3) Member, RAP-SAC, Centre for DNA Fingerprinting and Diagnostics, Hyderabad, India
4) Member, RAP-SAC, National Centre for Cell Science, Pune, India
5) Member, Jury for Sun Pharma Science Scholar Award, India
6) Member, Advisory Committee for BioTERM 2019, IIT Kanpur, India
7) Member, Scientific Advisory Committee (SAC), NIBMG, Kalyani, West Bengal, India
8) Inter-ministerial Expert Committee for finalization of Guidelines for Evaluation of Nanopharmaceuticals in India
9) Chairman, Local Advisory Committee, Regional Science City, Lucknow, India
10) Member, Advisory-cum-Monitoring Committee, Biotech Park, Lucknow, India
11) Member, Nanoscience Domain Expert Committee, MHRD STARS, India
12) Member, Drug Review committee, Directorate of Medical & Health, Uttar Pradesh, India
13) Chairperson, Committee to determine eligibility and qualifications for CSIR-UGC Net Exam, CSIR, India
14) Member, Technical Advisory Group on National Virtual Centre for Clinical Pharmacology, ICMR, India
15) Member, Expert Committee to Evaluate Proposal of Centre for Chemical Biology & Therapeutics (CCBT), DBT, India
16) Member, Committee for implementation of Roof Top Solar system in CSIR labs, India
17) Member, Expert Committee, Nanoscience Domain, MHRD – STARS Initiative, India
18) Member, Board of Governors, NIPER, Hajipur, India
19) Member, Project Screening Committee (PSC-II) relating to Research and Development (R&D) under Central Sector Scheme on Conservation, Development and Sustainable Management of Medicinal Plants of NMPB, India
20) Member, Steering Committee Meeting of the "Drugs from Sea" Program, India
21) Member, Award Committee, SGPGI, Lucknow, India
22) Member, Scientific Advisory Committee, Institute of Liver & Biliary Sciences, New Delhi, India
23) Member, Academic Council, Jawaharlal Nehru University, Delhi, India

C. Contribution to Science

1. Tumor suppressor p53 regulate Adipogenesis Epigenetically:

We discovered that p53 mediated regulation of expression of CARM1, a well-known transcriptional coactivator and arginine methyltransferase, negatively impacts fate of adipocyte differentiation. We demonstrated that p53 gets recruited to CARM1 promoter and represses its expression. When CARM1 expression is not repressed by p53, CARM1 induces and maintains PPARγ2 expression, which is essential for normal adipogenesis. Further transcriptome analysis and gene network modeling revealed multiple pathways along with lipid biogenesis pathway also to be modulated by p53 in preadipocytes. The experimental evidences on p53 mediated repression of CARM1 expression seem to bridge the mechanistic gap within the regulatory influence of p53 on PPAR-γ expression in adipocytes. This would illuminate our

Principal Investigator (Last, First, Middle):

understanding on metabolism of glucose and lipid at organismal level with a molecular basis and allow to address obesity and associative complications such as diabetes with better scientific preparedness.
Behera AK., Bhattacharya A, Vasudevan, and **Kundu TK.** p53 mediated regulation of Coactivator associated arginine methyltransferase 1 (CARM1) expression is critical for suppression of adipogenesis, **FEBS J 2018**;285(9):1730-1744.

2. Chromatin Dynamics Regulated by non-histone chromatin proteins:
We discovered that the highly abundant, multifunctional nuclear protein, PC4 is a *bonafide* chromatin component involved in the chromatin compaction and thereby genome organization and transcription regulation. My group has generated PC4 knockdown stable cell line and found that PC4 is indeed involved in genome stability. Interestingly, in a large number of breast cancer samples, PC4 expression was found to be down-regulated. Total knockout of PC4 is embryonic lethal. Presently, my group is working on organ-specific conditional knockout mice.
Swaminathan A, Delage H, Chatterjee S, Belgarbi-Dutron L, Cassel R, Martinez N, Cosquer B,Kumari S, Mongelard F, Lannes B, Cassel JC, Boutillier AL, Bouvet P, **Kundu TK.** Transcriptional Coactivator and Chromatin Protein PC4 Is Involved in Hippocampal Neurogenesis and Spatial Memory Extinction. **J Biol Chem: 2016**; 291(39):20303-14.
Sikder S, Kumari S, Mustafi P, Ramdas N, Padhi S, Saha A, Bhaduri U, Banerjee B, Manjithaya R, **Kundu TK.** Nonhistone human chromatin protein PC4 is critical for genomic integrity and negatively regulates autophagy. **FEBS J. 2019** Nov;286(22):4422-4442.

3. Histone Chaperones in the regulation of transcription and thereby diseases:
Our group is working on the human histone chaperone NPM1 and have found that it is a regulator of RNA polymerase II-driven chromatin transcription in an acetylation-dependent manner. We have shown that NPM1 was over-expressed and hyperacetylated in oral cancer. We have also found that NPM1 is a positive regulator of p300 autoacetylation. The mechanisms of transcription regulation by NPM1 and its gene specificity are being investigated now.
Gadad SS, Rajan RE, Senapati P, Chatterjee S, Shandilya J, Dash PK, Ranga U, **Kundu TK.** HIV-1 infection induces acetylation of NPM1 that facilitates Tat localization and enhances viral transactivation. **J Mol Biol 2011**; 410 (5): 997-1007.
Shandilya J, Senapati P, Dhanasekaran K, Bangalore SS, Kumar M, Hari Kishore A, Bhat A, Kodaganur GS, **Kundu TK.** Phosphorylation of multifunctional nucleolar protein nucleophosmin (NPM1) by aurora kinase B is critical for mitotic progression. **FEBS Lett. 2014**; 588(14): 2198-205

4. Small molecule modulators of chromatin modifying enzymes to elucidate differentiation pathways
Our group has also been actively working on the small molecule modulators of chromatin modifying enzymes for more than a decade now. Apart from several small molecule inhibitors of lysine acetyltransferases and arginine methyltransferase, we have also discovered the first known small molecule activator of p300/CBP lysine acetyltransferase, which could activate histone acetylation in mice brain and thereby enhance the neurogenesis process and spatial memory. At present the mechanisms of p300/CBP activation and neurogenesis is one of the key interests of my group. My laboratory has discovered new molecule to target, specific histone acetyl transferase PCAF and using this molecule, the gene network for muscle differentiation has been established. By employing one of the site specific inhibitors of the histone arginine methyl transferase CARM1, a new mechanism of glial differentiation was shown.
Modak R, Basha J, Bharathy N, Maity K, Mizar P, Bhat A, Vasudevan M, Rao V K, Kok W K, Nagashayana N, Taneja R, **Kundu TK.** Probing p300/CBP associated factor (PCAF)-dependent pathways with a specific small molecule inhibitor of lysine acetyltransferase. **ACS Chem Biol 2013**; 8(6):1311-23.
Selvi BR, Swaminathan A, Maheshwari U, Nagabhushana A, Mishra R, **Kundu TK.** CARM1 regulates astroglial lineage through transcriptional regulation of Nanog and posttranscriptional regulation by miR92a. **Mol Biol Cell: 2015; 26(2):316-26**

5. Specific KAT activator: implications in Nano-Biotechnology and Neurodegenerative Diseases:
The major emphasis has been given to the possible utilization of their recently discovered carbon nanospheres. The mechanism of its ability to cross the blood-brain barrier, delivery of the HAT activator molecule in the mammalian brain and targeted delivery of anti-neoplastic therapeutics in the solid tumor targeting the epigenetic modifications are the major focus of my laboratory. We have successfully conjugated a histone acetyltransferase activator with the CSP and could target it to mice brain. The conjugated molecule could induce histone hyperacetylation in hippocampus of mice brain thereby inducing neurogenesis and long term spatial memory formation. Recently we have shown that indeed the

Principal Investigator (Last, First, Middle):

specific activation of p300/CBP could result in almost complete recovery of memory in the neurodegenerative disease model. This activation could also dramatically lead to repairing of spinal injury in mice and rat.

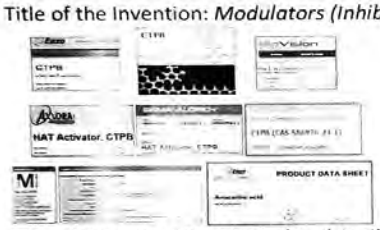
Chatterjee S, Mizar P, Cassel R, Neidl R, Selvi BR, Mohankrishna DV, Vedamurthy BM, Schneider A, Bousiges O, Mathis C, Cassel JC, Eswaramoorthy M, **Kundu TK**, Boutillier AL. A novel activator of CBP/p300 acetyltransferases promotes neurogenesis and extends memory duration in adult mice. **J Neurosci. 2013**;33(26):10698-712.

Swaminathan A, Delage H, Chatterjee S, Belgarbi-Dutron L, Cassel R, Martinez N, Cosquer B, Kumari S, Mongelard F, Lannes Chatterjee S, Cassel R, Schneider-Anthony A, Merienne K, Cosquer B, Tzeplaeff L, Halder Sinha S, Kumar M, Chaturbedy P, Eswaramoorthy M, Le Gras S, Keime C, Bousiges O, Dutar P, Petsophonsakul P, Rampon C, Cassel JC, Buée L, Blum D, **Kundu TK**, Boutillier AL. Reinstating plasticity and memory in a tauopathy mouse model with an acetyltransferase activator. **EMBO Mol Med. 2018**;10(11). pii: e8587.

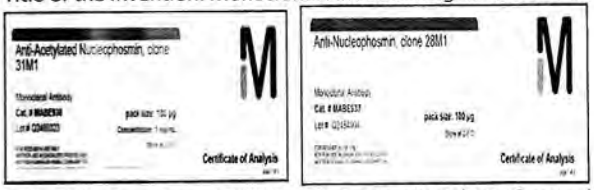
Hutson TH, Kathe C, Palmisano I, Bartholdi K, Hervera A, De Virgiliis F, McLachlan E, Zhou L, Kong G, Barraud Q, Danzi MC, Medrano-Fernandez A, Lopez-Atalaya JP, Boutillier AL, Sinha SH, Singh AK, Chaturbedy P, Moon LDF, **Kundu TK**, Bixby JL, Lemmon VP, Barco A, Courtine G, Di Giovanni S. Cbp-dependent histone acetylation mediates axon regeneration induced by environmental enrichment in rodent spinal cord injury models. **Sci Transl Med. 2019**;11(487). pii: eaaw2064.

6. Commercialized Products

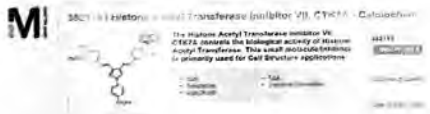
1. Title of the Invention: *Modulators (Inhibitors/Activators) of Histone Acetyltransferases.*



2. Title of the Invention: *Monoclonal Antibodies against NPM1 and Acetylated NPM1, and Process Thereof.*



3. Title of the Invention: *Inhibition of Histone Acetyltransferases by CTK7A and methods thereof.*



D. Research Support

1) **Investigating the role of BLM helicase as a global tumor suppressor: Understanding its regulatory loops and using the knowledge for therapeutic and clinical. Funding Agency: Department of Biotechnology, Government of India, Duration: 2015-2020. Collaborative research grant for Unit of excellence**
2) **Self-fluorescent cell permeable glucose derived carbon nanospheres as a brain targeting vehicle: Implications in drug delivery and imaging. Funding Agency: Department of Biotechnology, Government of India, Duration: 2016-2019**
3) **Virtual National Oral Cancer Institute, Funding Agency: Department of Biotechnology, Government of India, Duration: 2018-2021**
4) **"Next generation advanced therapies for fight β-hemoglobinopathies via rational intervention in γ-globin regulatory network". Funding Agency: Department of Biotechnology, Government of India, Duration: 2019-2023.**

CURRICULUM VITAE OF CHIEF SUPERVISOR

Name: **Dr. VIRENDRA ATAM**
PROFESSOR OF MEDICINE
Department Of medicine
KGMU Lucknow, U.P., INDIA

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QUALIFICATION:

1. MBBS K.G. MEDICAL COLLEGE Lucknow 1984
2. MD (Medicine) K.G. MEDICAL COLLEGE Lucknow 1989
3. REGISTERED for DM (NEUROLOGY) K.G.M.C. Lucknow 1989-1990

PRESENT STATES: HEAD AND PROFESSOR OF MEDICINE
HEAD DEPARTMENT OF ENDOCRINOLOGY
FACULTY INCHARGE I.D.H.

AREA OF INTREST: NEUROLOGY

THESIS SUPERVISED:

1. AS CHIEF SUPERVISOR: =32
2. AS CO- SUPERVISOR : = 47

PUBLICATIONS:

1. INTERNATIONAL: =25
2. NATIONAL: =67

ABSTRACTS PUBLISHED: = 37

CONFERNANCES ATTENDED:

Prof. Virendra Atam
Head.
Department of Medicine,
K.G.M.U., Lucknow

Medical Council Registration certificate
Dr. Virendra Atam, KGMU Lucknow

MEDICAL REGISTRATION CERTIFICATE
OFFICE OF THE MEDICAL COUNCIL, UTTAR PRADESH

CERTIFICATE No. 29089 Date 21 MAY 1985

Name ..... Atam, Virendra .....
Father's name Sri ..... Kham Dev Atam .....
Address M.I.G.A. Church Rd. O.R.Y. Colony, Lucknow
Qualification ..... MBBS (Luck) 85 .....
College ..... K.G. M.C. ..... University ..... Luck. .....
Year of passing examination ..... 1985 .....
Date and place of registration ..... 21-5-1985 ..... Lucknow
Schedule of the Indian Medical Council Act, 1956 ..... I .....
Underwent rotatory training from 1-5-84 to 31-4-85
at ..... G.M. and A. ..... Hospital ..... Lucknow .....

Registrar,

Specimen signature V. Kanaujia

(Seal)

Additional qualification registered on 13-3-90
M.D. (Medicine) Aug. 88
Lucknow University
Lucknow

Registrar Medical Council, U.P.

PSUP—AP—12 Chi. Sankaya-24-10-84—(2640)—1983—2000. (E)

14-05-2020

सी.एस.आई.आर.-केन्द्रीय औषधि अनुसंधान संस्थान, लखनऊ
(वैज्ञानिक तथा औद्योगिक अनुसंधान परिषद्)
सेक्टर 10, जानकीपुरम विस्तार, सीतापुर रोड, लखनऊ — 226 031 (भारत)
CSIR - Central Drug Research Institute
(Council of Scientific & Industrial Research)
Sector 10, Janakipuram Extension, Sitapur Road, Lucknow - 226 031 (India)
CSIR - Central Drug Research Institute, Lucknow

Brief Curriculum vitae

Dr MOHAMMAD MOONIS AKBAR FARIDI

MD, DCH, MAMS, FIAP, FNNF

Dean

Faculty of Medicine

Era University, Lucknow

and

Principal & Chief Medical Superintendent

Professor of Pediatrics

Era's Lucknow Medical College, Lucknow

Academic Qualification : **MBBS, MD, DCH**

Area of Special Interest : NEONATOLOGY

Teaching Experience : 39Years

Post Graduate : 35½ years

Teaching Experience

Course Director

WHO/UNICEF/IBFAN/BPNI

Infant & Young Child Feeding Counseling Course

Fellow

Indian Academy of Pediatrics [FIAP] (1999)

National Neonatology Forum of India [FNNF] (2012)

Visiting Professor

BP Koirala Institute of Health Sciences, Dharan, Nepal (Since 2003)

Ali Yavarjung Institute of Hearing Handicaps, New Delhi (Since 2007)

American University of Barbados School of Medicine, Bridgetown (2018)

Past President

Indian Academy of Pediatrics Delhi State (2006)

National Neonatology Forum, Delhi State (2011-12)

National Vice-President

IAP IYCF Chapter (2012-14)

Zonal Coordinator [North Zone]

IAP Postgraduate Quiz Competition (Since 2007-2016)

National Executive Board Member

Indian Academy of Pediatrics (2014, 2017)

National Co-convener

IAP Undergraduate Quiz Competition (2014-15)

Member Ethics Committee for Human Research

GTB Hospital Delhi (2010-2017)

Eras Lucknow Medical College, Lucknow (since 2013)

Chairman, SDN Hospital Ethics Committee (since 2017)

Associate Editor

Human Vaccine & Immunotherapeutics (2016)

Guest Editor

A. Publications (Total) : 196

Papers published in the International Index Journals : 77

Papers published in the National Index journals : 103

Paperpublished in the National Non-index journal : 07

Paper published in the International Non-index Journal : 01

Abstracts published in Index journals : 08

B. Chapters in Books (Total) : 24

C. Books published : 02

D. PG theses guided : 80

E. Citation indices [Google Scholar]All Since 2015

(Accessed on May 10, 2020)

Total Citations : 25791249

h-index : 2920

i10-index : 6938

F.Citation indices [ResearchGate]

RG Score : 36.82

(Accessed on May 10, 2020)

Research Interest[RI] : 997.2

RI Rating : >95% of all RG researchers

h-index : 23

Publication read : 26057

Total Citations : 1787

G. Reviewer

International Journals : 16

National journals :06

H. Editor

Associate Editor [International journal] : 01

Section Editor [International Journal]:01

Guest Editor [National Journal]:01

MEDICAL COUNCIL OF INDIA

WAN-E-GHALIB MARG, KOTLA ROAD, NEW DELHI-110002

Certificate of Registration of Additional Qualification(s) u/s 26 of the Indian Medical Council Act, 1956

No. 773 Date 29.5.1989

I hereby certify that the following additional qualification (s) as shown in column 4 below has/have been entered in the Indian Medical Register.

Name	Qualifications as entered in the Indian Medical Register	Regn. No Date and State Medical Council with which registered.	*Additional qualification entered in the Indian Medical Register	Address
1	2	3	4	5
FARI I, MOH MOONIS AKBA R	M.B.B.S. (U.Aligarh)1975	19386 18.6.1976 U.P.	D.C.H. (Aligarh Muslim Univ.) 1978. M.D. (Paed.) (Aligarh Muslim Univ.)1982	(i) Permanent D-18,G.T.B. Hospital Campus, Delhi-110032. (ii) Present

MEDICAL COUNCIL OF INDIA 1933

(P.S.Jain)
Registrar,
Medical Council of India

* Only recognised qualifications,(i.e. included in the schedules) are mentioned.

BIODATA OF THE INVESTIGATOR

1. Name:Dr. Vikram Singh
2. Designation: Professor
3. Complete Postal Address: Department of General Medicine Dr. Ram Manohar Lohia Institute of Medical Sciences Lucknow .
   E-mail, gmail.com Phone no: 9680005076
4. Date of Birth: 23-Dec-1979
5. Educational Qualification : Degrees obtained (Most recent should come first)

Degree	Institution	Field(s)	Year
M.D	Institute of Medical Sciences (IMS) Banaras Hindu University, Varanasi	Internal Medicine	2006
M.B.B.S	Institute of Medical Sciences (IMS) Banaras Hindu University, Varanasi		2002

6. Job Experience (*Current and previous positions including academic appointments «most current date first)*

Duration	Institution	Particulars of work done
Associate Professor	DR RMLIMS Lucknow	09.03.2017-Ongoing
Assistant Professor	DR RMLIMS Lucknow	14-08-2013-10-04-2017
Assistant Professor	V.C.S.G. Government Medical Science and Research Institute	14-12-2009-13-08-2013

7. Research specialization (Major scientific fields of interest):
   Hypertension, Diabetes
8. Summary of clinical research experience(preferably in last 5 years)

Role in the Study (PI/ Co-PI)	Title of study	Funding agency	Duration
PI	Role of Aspirin on inflammatory mediators in type 2 Diabetes Mellitus	AIIMS	2019 To Ongoing
PI	Role of Hs CRP and Reversal of Serum Albumin/Globulin ratio in	AIIMS	2018 to 2019

	differentiating Tuberculosis from Community acquired Pneumonia		

9. Important recent publications (last 5 years, with titles and References), including papers In press:

1-Vikram Singh,Mridu Singh, PS singh, Pancytopenia: Etiologies and Manifestation in Eastern India;IJRMS:2017:Nov;5(11)

2-Vikram Singh, Mridu Singh, Anil Joshi, Chitra Joshi; Prevalence of Different components of Metabolic Syndrome in Type 2 Diabetics attending tertiary care hospital In Himalayan Region,Int J Res Med Sci 2017 Dec,5(12)

3-Vikram Singh, Arup K. Misra, Mridu Singh, Naresh K. Midha, Bharat Kumar, Sneha Ambwani, Gopal K. Bohra, Pramod K. Sharma;An open□label, randomized, 10 weeks prospective study on the efficacy of vitamin D (daily low dose and weekly high dose) in vitamin D deficient patients Journal of Family Medicine and Primary care (Accepted)

4-Sundar S, Mehta H, Chhabra A, **Singh V**, Chauhan V, Desjeux P, Rai M;Amphotericin B colloidal dispersion for the treatment of Indian visceral leishmaniasis. Clin Infect Dis. 2006 Mar 1;42(5):608-13.

5- S sunder, K singh, R Maurya, , A Chabra,V Singh, M Rai; Serological diagnosis of Indian Visceral .Leishmaniasis: Direct agglutination test verses RK39 strip test. Transaction of the Royal Society of tropical medicine and Hygiene 06/2006;100(6)533-7

6-Sundar S, Kumar K, Chakravarty J, Agrawal D, Agrawal S, Chhabra A, **Singh V.**Cure of antimony-unresponsive Indian post-kala-azar dermal leishmaniasis with oral miltefosine. Trans R Soc Trop Med Hyg. 2006 Jul;100(7):698-700.

11-05-2020

MEDICAL REGISTRATION CERTIFICATE

OFFICE OF THE MEDICAL COUNCIL, UTTAR PRADESH
5, SARV PALLI , MALL AVENUE ROAD, LUCKNOW

Certificate No 047183 Date - 5 FEB 2003

Name SINGH VIKRAM

Father's Name Sri RANA PRATAP SINGH

Address 4/59 VISHAL KHAND GOMTINAGAR LUCKNOW

Qualification M.B.B.S (B.H.U.) 2003

College I.M.S. VARANASI University B.H.U.

Year of Passing Examination DEC 2002

Date & Place of Registration - 5 FEB 2003 Lucknow (U.P.)

Schedule of the Indian Medical Council Act, 1956 2

Underwent rotatory training from 1.1.2004 To 31.1.2005

at S.S.L. Hospital VARANASI CIVIL HOSPITAL

(Specimen signature overleaf)

Registrar

मेडिकल कौंसिल उत्तर प्रदेश

Name : **Dr. Vivek Vidyadhar Bhosale**

Address : Division of Toxicology and Experimental Medicine
CSIR-Central Drug Research Institute
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Date of Birth: 22nd September 1978

ACADEMIC PROFILE:

- **Course** : **M.D. (Master of Medicine), Awarded 2008**

Specialisation : Pharmacology

University/Institute: Government Medical College, Miraj, MH, India.

- **Course** : **M.B.B.S. (**Bachelor of Medicine and Bachelor of Surgery**), Awarded 2002.** University/Institute:University of Pune, MH,

Medical Council Registration Number (MCI): 2002072602 (MMC)

PREVIOUS POSTING:

Resident doctor: Govt Medical College, Miraj from Year 2007-2008

Medical Advisor FDC Ltd Mumbai from year 2009-2010

CURRENT POSITION: From October 2010

Senior Scientist, Division of Toxicology and Experimental Medicine
CSIR-Central drug Research Institute. From October 2010

SELECTIVE PAPER PRESENTATION

- Chhonker YS, Bhosale VV, Sonkar SK, Chandasana H, Kumar D, Vaish S, Choudhary, SC, Bhadhuria S, Sharma S, Singh RK, Jain GK, Vaish AK, Gaur SPS, Bhatta RS. 2017. Assessment of clinical pharmacokinetic drugdrug interaction of antimalarial drugs α/β- arteether and sulfadoxine-pyrimethamine. Antimicrob Agents Chemother 61:e02177-16. https://doi.org/10.1128/AAC.02177-16.PMID: 28674061
- Jain M, **Bhosale V**, Tripathi D, Singh H, Pal N, Hanif K, Jagavelu K. Antihypertensive drugs aliskiren, nebivolol, and olmesartan reduce hypertension by reducing endothelial microparticle and regulating angiogenesis. J Cardiovasc Pharmacol. 2017 May 9. doi: 10.1097/FJC.0000000000000503. PMID: 28498232

- Sonkar SK, Bhutani M, Sonkar GK, Pandey SK, Chandra S, **Bhosale V**. Vitamin D levels and other biochemical parameters of mineral bone disorders and their association with diastolic dysfunction and left ventricular mass in young nondiabetic adult patients with chronic kidney disease. Saudi J Kidney Dis Transpl. 2017 Jul-Aug;28(4):758-763. PMID: 28748877
- Gupta S, Kushwaha VS, Verma S, Khan H, Bhatt ML, Husain N, Negi MP, **Bhosale VV**, Ghatak A. Understanding molecular markers in recurrent oral squamous cell carcinoma treated with chemoradiation. Heliyon 2016, 2(12), e00206. http://doi.org/10.1016/j.heliyon.2016.e00206. PMID: 27981249
- Vinod kumar Tewari, Vivek Bhosale, Rakesh Shukla, Hari kishan das Gupta, Sheeba. Intracarotid Sodium Nitroprusside on 5th Post Ischemic Stroke Day in Middle Cerebral Artery Occlusion Rat Model. Accepted in Journal of Clinical and Diagnostic Research, 2017. Aug;11(8):AF01-AF04.DOI: 10.7860/JCDR/2017/28085.0000
- **Vivek V. Bhosale**, S.C. Inamdar, Karande V.B., Burute S.R., Murthy M.B., Ghatak A.. BENEFICIAL EFFECTS OF NEBIVOLOL IN COMPARISON WITH ATENOLOL ON SAFETY AND TOLERABILITY IN ESSENTIAL HYPERTENSION. Journal of Clinical and Diagnostic Research Year : 2014 Month : June Volume : 8 Issue : 6 Page : HC01 - HC04. PMID: 25120998
- **Vivek V. Bhosale**, O.P. Asthana, S.P.S. Gaur. *Efficacy and Safety of Herbal Spermicidal Contraceptive Consap*. Current science 2013. Vol. 104, No. 12, Pages 1701-1703.
- **Vivek Bhosale**, K C Jindal, Sunil Tolat, Mahendra Kura, Satish Udare, Vinay kulakarni, Bela Shah, Ranjan Raval, Yogesh marfatia. Comparative study of the efficacy and safety of Acyclovir 1200mg sustained release versus Acyclovir 800mg immediate release in immunocompetent patients with uncomplicated Herpes Zoster. The Indian practitioner 2010 vol.63 No.10 Page 759
- **Bhosale, Vivek V**.; Gaur, S. P. S. Adverse Drug Reaction Monitoring. Current Science 2011 Vol 101 No.8 Pages 1024-27
- Satyendra Kumar Sonkar, Anil Kumar, Neeraj Kumar Singh, Gyanendra Kumar Sonkar, Sant Pandey, **Vivek Bhosale**. Role of Hepcidin on Response of Erythropoietin Stimulating Agents in Anaemic Advanced Chronic Kidney Disease Patients. Journal of Clinical & Diagnostic Research . Oct2018, Vol. 12 Issue 10, p14-16. 3p.
- Banerjee D., Jain T., Bose S., **Bhosale V**. (2018) Importance of Probiotics in Human Health. In: Rani V., Yadav U. (eds) Functional Food and Human Health. Springer, Singapore

27.12.2018.

(Dr.Vivek Vidyadhar Bhosale)