MINUTES OF THE 42nd MEETING OF THE CLINICAL STUDIES COMMITTEE TO BE HELD ON 03RD MAY, 2023.

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The 42nd meeting of the Clinical Studies Committee was held on 03rd May, 2023 in the Committee Room, Drug Regulatory Authority of Pakistan, G-9/4, Islamabad, through Zoom. The meeting was Chaired by Dr. Obaidullah, Director Pharmacy Services. The meeting was started with recitation of the Holy Verses.

The meeting was attended by the following members: -

i.	**Dr. Obaidullah**	Director Pharmacy Services Division **Chairman CSC**,.		Online through Zoom
ii.	**Ahsan Ul Haq Athar**	Deputy Director, Pharmacy Services Division **Secretary, CSC**.		In-person
iii.	**Prof. Dr. Fazal Subhan**	Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar, Khyber Pakhtunkhwa.	Member	Online through Zoom
iv.	**Prof. Munawar Alam Ansari.**	Professor of Pharmacology, Dean Faculty of Pharmacy, Liaquat University of Medical Sciences, Jamshoro. **(Sindh)**	Member	-do-
v.	**Prof. Dr. Saeed Ahmad Khan**	Professor of Medicine Bolan Medical College Quetta presently serving as head of medicine department Jhalawan medical college Khuzdar, Balochistan.	Member	-do-
vi.	**Dr. Mirza Tasawer Baig**	Associate Professor in the Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi & Clinical Pharmacist at Dr. Ziauddin Hospital, Karachi, Sindh.	Member	-do-
vii.	**Dr. Faiza Bashir**	Chairman, Pakistan Health Research Council or his/her nominee, Islamabad.	Member	-do-
viii.	**Mr. Waqas Latif**	Data Analyst/Biostatistician in Quality Enhancement Cell (QEC) at University of Health Sciences, Lahore, Punjab.	Member	-do-

2. Mr. Nouman Yousuf, Malik Muhammad Asad and Shafqat Hussain Danish assisted the Committee and Secretary in presentation of the agenda.

AGENDA ITEM I:

SERIOUS ADVERSE EVENT REPORTED FOR CLINICAL TRIAL TITLED, "A MULTI-CENTER, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED, PHASE-III CLINICAL STUDY TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF SARS-COV-2 BIVALENT mRNA VACCINE (LVRNA021) AS BOOSTER IN PARTICIPANTS AGED 18 YEARS AND OLDER WHO COMPLETED PRIMARY/1 BOOSTER DOSE(S) OF SARS-COV-2 VACCINATION" RECEIVED FROM IBBPS OF DOW UNIVERSITY OF HEALTH SCIENCES, KARACHI.F. No.03-35/2023-CT (PS)

It is submitted that, subject trial was approved by the CSC in its 39th Meeting, held on 28th February, 2023. Summary of the trial application & decision is reproduced as under:

Dr. Muneeba Ahsan Sayeed, CNIC number: 42201-0461114-4, Principal Investigator (PI) & Assistant Professor, Department of Infectious Diseases, Sindh Infectious Diseases Hospital & Research Center, NIPA, Karachi, dated 17th February 2023, wherein request has been made for approval of subject 'Clinical Trial' on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide challan no. 2988200289, dated 16th February 2023. The trial is also enlisted on the Chinese Trial Registry with identification number ChiCTR2200063934 dated 21-09-2022 with the trial name "A preliminary exploratory cohort study evaluating the safety, tolerability and immunogenicity of bivalent novel coronavirus mRNA vaccine (LVRNA021) in Chinese people aged 18 years and older" and linked herewith as china clinical trials registry - a first-level registry of the world health organization's international clinical trial registry platform (chictr.org.cn).

2. The details regarding trial, sponsor & responsible party is as under:

i. Sponsor: AIM Vaccine Co., Ltd., China
ii. Collaborators: Ningbo Rongan Biological Pharmaceutical Co., Ltd., China
LiveRNA Therapeutics Inc.
iii. Number of subjects to be recruited: 9,800 participants approx.
iv. Anticipated cost of the project: PKR 343,595,220/-

3. Purpose of trial:

The outbreak and epidemic of COVID-19 has put a heavy economic pressure and medical _burden on people worldwide and poses a serious threat to human survival and health, demonstrating an urgent need for efficacious vaccines. The COVID-19 vaccines that are currently in development or have been approved are expected to provide at least some protection against new virus variants because these vaccines elicit a broad immune response involving a range of antibodies and cells. Therefore. changes or mutations in the virus should not make vaccines completely ineffective. However, the recent evolution of SARS-Co V-2 is resulting in an emergence of new virus variants with multiple mutations in the S protein, which might be associated with the lower efficacy of some of the current vaccines. Therefore, there is a need to continue research including new approaches, such as evaluation of booster doses, to overcome waning immunity and/or the development of modified vaccines.

This phase 3 study is a multicenter, randomized, blinded, placebo-controlled design to evaluate the efficacy, immunogenicity, and safety of 1 booster dose of SARS-CoV-2 bivalent mRNA vaccine (LVRNA021) in participants aged 18 years and older who completed primary/I booster dose(s) ofSARS-CoV-2 vaccination.

The primary objective of the study is to evaluate the protective efficacy of LVRNA021 in the prevention of first episodes of virologically confirmed symptomatic cases of COVID-19 of any severity occurring from 14 days after booster vaccination.

4. OVERALL STUDY DESIGN AND TREATMENT PLAN

This is a multicenter, randomized, blinded, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of LVRNA021, against COVID-19 in participants aged 18 years and older.

About 9,800 participants aged 18 years and older who completed primary/1 booster dose(s) of SARS-CoV-2 vaccination (including primary series of inactivated vaccine, mRNA vaccine. adenovirus vaccine or 1 homologous/heterologous dose of booster) whose last dose was given ≥ 6 months. Participants will be tested for SARS-CoY-2 RT-PCR at baseline and RT-PCR-positive participants will be excluded from the study and they must not have documented history of SARS-CoV-2 infection within 6 months before enrolment. About 10%-20% of participants 60 years and older will be included. Participants will be randomized in a 1:1 ratio, the study vaccine group will receive 1 dose of the study vaccine on Day 0, and control group will receive 1 dose of placebo on Day 0.

This study is an endpoint event-driven study with an adaptive design and the primary endpoint is 162 confirmed cases. which protection efficacy is calculated based on the accumulated number of cases in the study and control groups. using the formula VE= 100* (l- risk ratio) (risk ratio = incidence in the study group/incidence in the control group). An interim analysis will be conducted based on the accumulation of approximately 2/3 (n= 109) of the total anticipated primary endpoints. If the study vaccine demonstrates statistically significant vaccine efficacy, participants will have a chance to choose their blinding status. Participants who decide to be un-blinded and those in the placebo group will be receiving marketed booster vaccination according to local regulations and guidance.

Clinical Endpoint Committee (CEC) will be established to make the final determination on virologically-confirmed COVID-19 cases and severity grading. OSMB will be established as well to independently and continuously monitor the safety and efficacy data of the study vaccine and to provide recommendations on interim analysis results. DSMB will also periodically review safety data or conduct additional safety assessments at the request of the sponsor in un-blinded status.

Study type	Investigational (Clinical Trial)
Estimated Enrollment :	9,800 participants.
Allocation:	Randomized, Blinded
Intervention Model:	Parallel Assignment
Masking:	Double (Participant & Investigator)
Primary Purpose:	Treatment
Duration :	20-months

5. Proposed Clinical Trial Sites and Principal Investigator are as follows:

Sr.#	Proposed Site(s) of CT	Investigator
1.	Prof, Dr. M. Raza Shah **National Principal Investigator,** General Manager-CBSCR-ICCBS, H.E.J. Research Institute of Chemistry University of Karachi	
2.	IBBPS-Dow University Hospital, DUHS, Karachi.	SADIA ASIM **(Site-PI)**, Director IBBPS, DUHS, Karachi
3.	Sindh Infectious Disease Hospital and Research Center, Karachi.	Dr. Muneeba Ahsan Sayeed **(Site-PI),** Assistant Professor, Department of Infectious Diseases, Sindh infectious Diseases Hospital & Research Center, NIPA, Karachi.
4.	Al-Shifa Eye Trust Hospital, Rawalpindi	Prof Dr. Ume Sughra **(Site-PI)**; Al-Shifa Research Center, Al-Shifa Trust, Eye Hospital. Rawalpindi
5.	Central Park Teaching Hospital, Lahore.	Dr. Muhammad Ahmad **(Site-PI)**, (Director-CTU) Associate Professor & HOD of Pulmonology and Critical Care.
6.	Maroof International Hospital, Islamabad.	Dr. Mir Abdul Waheed **(Site-PI)**, Medical Director, Consultant & Head of Emergency Medicine, Islamabad.
7.	Creek General Hospital, Karachi.	Prof. Dr. Farhat Bashir **(Site-PI)**, Professor of Medicine, Clinical Coordinator & Manager (CTU-CGH), UMDC, Karachi.
8.	Rehman Medical Institute, Peshawar.	Dr. Sajjad Ali **(Site-PI)**, Consultant Internal Medicine and Infectious Diseases, Associate Professor of RMI Peshawar.

6. Material Transfer Agreement (MTA) is entered into by and among: -

i. DOW University of Health Sciences, OJHA Campus, Karachi. (Sending Party)
ii. Nanjing Vazyme Testing Technology Co. ltd., Building C2, Red Maple Technology Park, Kechuang Road Economy & Technology Development Zone, Nanjig, China. (Receiving Party)

iii. Metrics Research (Pvt) ltd., Plot# B-10, Block 16, KDA Scheme no.24, WCHS, Gulshan e Iqbal Karachi. **(CRO).**

7. Identity of investigational Vaccine: -

The investigational vaccine is SARS-CoV-2 Bivalent mRNA Vaccine: the placebo is normal saline. **Both were provided by AIM Vaccine Co.; Ltd.** Details of IMPs are as follows:

Item	**Investigational Vaccine**	**Placebo**
Drug name	SARS-CoV-2 Bivalent mRNA Vaccine (LVRNA021)	Normal Saline
Strength	100 µg/1ml/Vial	1.0 ml/Vial
Batch No	DP202208020	20220801
Description	Slightly opalescent clear liquid	Clear liquid
Storage & Transportation	-20±5°	
Shelf Life	12 months (tentatively)	
Supplier	AIM Vaccine Co. Ltd., China.	
Manufacturer	Ningbo Rongan Biological Pharmaceutical Co., Ltd., China	
Route of administration	Intramuscular injection into the lateral deltoid muscle.	
Immunization Procedure	Intramuscular injection on days 0 (either Active/Placebo).	

8. The details of the submitted documents and summary of the application is as under;

Sr. No.	**Document**	**Remarks**
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs. 200,000/- deposited vide challan no. 2988200289, dated 16th February, 2023
3	Investigator Brochure (s)	IB of LVRNA021, Version 1.2, Dated: 15th February, 2023 is attached.
4	Final protocol	Attached LVRNA021-III-01, Version 1.0, dated 06th January, 2023.
5	Informed consent and participant information sheet (Urdu to English)	Attached.
6	List of participating countries	Pakistan only.
7	Phase of trial.	Phase – III
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	• Active: 4900 x 15% = 735; Total Import Quantity: 4900 + 735 = **5635** • Placebo: 4900 x 15% = 735; Total Import Quantity: 4900 + 735 = **5635**
9	Site of the trial	i. Dow University of Health Sciences, Ojha Campus Karachi. ii. Sindh Infectious Disease Hospital and Research Center Karachi iii. Al-Shifa Hospital Eye Trust, Rawalpindi iv. Central Park Teaching Hospital, Lahore v. Maroof International Hospital, Islamabad. vi. Creek General Hospital, Karachi vii. Rehman Medical Institute, Peshawar
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB approval of following CTS are attached: i. Dow University of Health Sciences, Ojha Campus Karachi, dated 16th February, 2023 is attached. (652-653/Corr.)

		ii. Sindh Infectious Disease Hospital and Research Center Karachi, dated 16th February, 2023 is attached. (652-653/Corr.) iii. Al-Shifa Hospital Eye Trust, Rawalpindi, dated 11th January, 2023 is attached. (654-655/Corr.) iv. Central Park Teaching Hospital, Lahore dated 23rd January, 2023 is attached. (656-657/Corr.) v. Creek General Hospital, Karachi, dated 09th February, 2023 is attached. (658-659/Corr.) vi. Maroof International Hospital, Islamabad. dated 25th January, 2023 is attached. (660-661/Corr.) vii. Rehman Medical Institute, Peshawar dated 24th January, 2023 is attached. (662-663/Corr.)
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter No. **Ref: No.4-87/COVID-135/23/1292** 4-87/COVID-122/22/672, dated 23rd February, 2023 for a period of **Six months** is attached.
12	CV's of the Investigators	CVs of following (National PI & Site-PIs) experts are attached. i. **Prof, Dr. M. Raza Shah (National-PI),** CBSCR-ICCBS, H.E.J. Research Institute of Chemistry University of Karachi ii. SADIA ASIM, Director IBBPS, DUHS, Karachi (Site-PI) iii. **Dr. Muneeba Ahsan Sayeed(Site-PI),** Assistant Professor, Department of Infectious Diseases, Sindh infectious Diseases Hospital & Research Center, NIPA, Karachi. iv. Prof Dr. Ume Sughra (Site-PI); Al-Shifa Research Center, Al-Shifa Trust, Eye Hospital. Rawalpindi v. **Dr. Muhammad Ahmad (Site-PI),** (Director-CTU) Associate Professor & HOD of Pulmonology and Critical Care. Central Park Teaching Hospital, Lahore. vi. **Dr. Mir Abdul Waheed (Site-PI),** Medical Director, Consultant & Head of Emergency Medicine, Islamabad. Maroof International Hospital, Islamabad. vii. **Prof. Dr. Farhat Bashir (Site-PI)**, Professor of Medicine, Clinical Coordinator & Manager (CTU-CGH), UMDC, Karachi. Creek General Hospital, Karachi. viii. **Dr. Sajjad Ali (Site-PI),** Consultant Internal Medicine and Infectious Diseases, Associate Professor of RMI Peshawar.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following manufacturer(s) are attached: • M/s Ningbo Rongan Biological Pharmaceutical Co., Ltd., China.
14	Pre-clinical/clinical safety studies	Attached. Attached (IB Page 06-44/Corr.)
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Attached.
19	Name of Monitors & Clinical Research Associate	Attached.
20	Evidence of registration in country of origin.	**Not applicable.**
21	Copy of registration letter (if registered in Pakistan)	Not applicable.
22	Sample of label of the investigational product / drug.	Attached.

22	Duration of trial	20 Months
23	Undertaking on Stamp paper	Attached.

05. Further it is informed that applicant also provided following documents related with test sample collection, handling, storage & its transportation to designated Bio-analytical Laboratory (i.e. Nanjing Vazyme Testing Technology Co. ltd., Building C2, Red Maple Technology Park, Kechuang Road Economy & Technology Development Zone, Nanjig, China):

- Material Transfer Agreement.

Decision:

The CSC after detailed discussion and deliberation decided to:

- *Approve the Clinical Trial titled, "A Multi-Center, Randomized, Blinded, Placebo-Controlled, Phase-III Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of SARS-COV-2 Bivalent mRNA Vaccine (LVRNA021) as Booster in Participants aged 18 Years and Older Who Completed Primary/1 Booster Dose(s) of SARS-COV-2 Vaccination", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site(s):*

  i. *Dow University of Health Sciences, Ojha Campus Karachi. (CTS-0068)*
  ii. *Sindh Infectious Disease Hospital and Research Center Karachi. (CTS-0069)*
  iii. *Al-Shifa Hospital Eye Trust, Rawalpindi. (CTS-0044)*
  iv. *Central Park Teaching Hospital, Lahore. (CTS-0049)*
  v. *Maroof International Hospital, Islamabad. (CTS-0045)*
  vi. *Creek General Hospital, Karachi. (CTS-0077)*
  vii. *Rehman Medical Institute, Peshawar. (CTS-0060)*

- *A total of 9800 Subjects will be enrolled in the study & following mentioned quantities of IMP will be imported after getting necessary approval/NOC from concerned DRAP field office:*
- ***Identity of investigational Vaccine**: -*
  The investigational vaccine is SARS-CoV-2 Bivalent mRNA Vaccine: the placebo is normal saline. Both were provided by AIM Vaccine Co.; Ltd., China. Details of IMPs are as follows:

Item	***Investigational Vaccine***	***Placebo***
Drug name	*SARS-CoV-2 Bivalent mRNA Vaccine (LVRNA021)*	*Normal Saline*
Strength	*100 µg/1ml/Vial*	*1.0 ml/Vial*
Batch No	*DP202208020*	*20220801*
Description	*Slightly opalescent clear liquid*	*Clear liquid*
Storage & Transportation	*-20±5°*	
Shelf Life	*12 months (tentatively)*	
Supplier	*AIM Vaccine Co. Ltd., China.*	
Manufacturer	*Ningbo Rongan Biological Pharmaceutical Co., Ltd., China*	
Route of administration	*Intramuscular injection into the lateral deltoid muscle.*	
Immunization Procedure	*Intramuscular injection on days 0 (either Active/Placebo).*	

a. Wastage and Damage% will be 15%:

- *Active: 4900 x 15% = 735; Total Import Quantity: 4900 + 735 =* ***5635***
- *Placebo: 4900 x 15% = 735; Total Import Quantity: 4900 + 735 =* ***5635***

- SAE, reported from DUHS & SIDH by Dr. Beenish Sayyad, Co-Investigator, Dow University of Health Sciences (DUHS), OJHA Campus Karachi.

6. Accordingly, trial registration letter (CT-0052) was issued on 08th March, 2023. Serious Adverse Events from following two sites has been received, application & SAEs summary is reproduced as under:

I. <u>SAE reported from DUHS by Dr. Beenish Sayyad, Co-Investigator, SIDH, Karachi and DUHS, OJHA Campus Karachi.</u>

Respected Sir,
Reference to the subject enclose please find the adverse event reports of subject 5020022 in, "A MULTI-CENTER, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED, PHASE-III CLINICAL STUDY TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF SARS-COV-2 BIVALENT mRNA VACCINE (LVRNA021) AS BOOSTER IN PARTICIPANTS AGED 18 YEARS AND OLDER WHO COMPLETED PRIMARY/1 BOOSTER DOSE(S) OF SARS-COV-2 VACCINATION" on-ongoing at M/s. Dow University of Health Sciences, Ojha campus Karachi (CTS-0068) & M/s. Sindh Infectious Diseases Hospital, Karachi, Pakistan (CTS-0069)-DUHS for reference.
Looking forward to your kind consideration as usual.

- *<u>DESCRIBE REACTION(S) (including relevant test/lab data):</u>*

Subject S020022 was enrolled in study LVRNA021. He signed the informed consent on 01/APR/2023 According to his demographics his date of birth is 1/MAR/1980, race is Asian, ethnicity is Urdu speaking.

Date of randomization is 03/APR/2023 and random ID is 01292. On 5th /Apr/2023 trial site received information from subject's department as subject himself is the employee of DUHS. Then the site contacted the subject's family and according to subject's wife He suffered with stroke at home on evening of 4th/Apr/2023. He developed Right sided facial weakness with slurred speech and difficulty in swallowing.

He was immediately shifted to JPMC where he was given initial treatment till his condition was stable. He is now shifted to Memon Medical Institute ICU. There is no history of Diabetes Mellitus, Hypertension, Ischemic Heart Disease or any other known risk factors

II. <u>SAE, reported from DUHS & SIDH by Dr. Muhammad Ahmad, Principal Investigator, Central Park Teaching Hospital, 31-Km Ferozepur Road Kahna Nau Lahore</u>

Subject: SAE Intimation of s040224 of DRAP Approved Clinical Trial (CT-0052) LVRNA021-lll-01

This letter is to inform that SAE occurred at the Central Park Teaching Hospital in clinical trial, "A MULTI-CENTER, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED, PHASE-III CLINICAL STUDY TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF SARS-COV-2 BIVALENT mRNA VACCINE (LVRNA021) AS BOOSTER IN PARTICIPANTS AGED 18 YEARS AND OLDER WHO COMPLETED PRIMARY/1 BOOSTER DOSE(S) OF SARS-COV-2 VACCINATION".
Subject with screening number 5040224, was admitted to a tertiary care hospital on 08-APR-2023. The subject was diagnosed as a case of Acute Myocardial Infarction, with symptoms of chest pain, sweating & breathlessness and confirmed on ECG. The subject underwent Angiography, which confirmed the blockage of right circumflex artery and therefore, underwent angioplasty with stenting. The subject was discharged on 11-APR-2023 in a stable condition, after recovering from the Acute Myocardial Infarction. Investigator became aware of the SAE when the subject contacted them after being discharged from the hospital. This is an initial report more data is been collected and will be reported in the final report. The initial report is attached to this letter with the known details of the SAE to
date.

If you have any queries kindly contact me and I will address them. Looking forward to your acknowledgment. Kind Regards.

III. SAEs, REPORTED FROM CREEK GENERAL HOSPITAL, KARACHI BY PROF. DR. FARHAT BASHIR, PRINCIPAL INVESTIGATOR (LVRNA021)

Dear Concerned,

This communication is to inform you about the DRAP approved study titled "A Multicenter, Randomized, Blinded, Placebo-controlled, Phase 3 clinical study to Evaluate the Efficacy, safety and lmmuno8enicity of SAR9CoV-2 Bivalent mRNA Vaccine (wRNAO21) as Booster in Participants Aged 18 Years and Older Who Completed Primary/1 Booster Dose(s) of SARICoV-2 vaccination".

The participant (screening number so3o3o7), who gave consent on 07/Apr/2023 and was randomized after, screening on 08/Apr/2023, was administered the IP on 8/Apr/2023. He presented with fever and severe myalgia of grade 3 on 9/Apr/2023, he was admitted and managed with acetaminophen, intravenous hydration and intravenous ceftriaxone. He improved within 12 hours and was afebrile and completely mobile. He was kept under observation fora further 12 hours and then was discharged on 11/Apr/2023.

7. Relevant provision and powers of Clinical Studies Committee under the Bio-Study Rules, 2017 are as under:

13 (4)(d) grant, reject or suspend approval of a clinical trial and BA or BE study;

13 (8) The CSC shall also consider relevant clinical trial decisions, reports or other information from stringent regulatory authorities and regional or international bodies like WHO, ICH and others. Any application for approval or registration of clinical trial will not undergo in the assessment process, if the same at any stage, has already been rejected, suspended or put on hold due to any reason, in ICH member countries or stringent regulatory authorities and shall be rejected during the process of screening.

16 (2) If at any time, for safety reason or any other ground a clinical trial is withdrawn or suspended anywhere in the world, the sponsor in Pakistan shall, forthwith, inform CSC, all participating investigators and all reviewing institutional review boards, together with the reasons for such withdrawal or suspension, within seven calendar days. The inventories of the investigational products shall be maintained and its safe custody shall be ensured.

16 (3) The CSC on having information with regard to the safety of the subject or any other ground, after giving an opportunity of personal hearing to the registration or approval holder, may at its own motion withdraw or suspend the clinical trial.

18 (a) proceeding for canceling or suspending or revision of condition of license or modification of a license or approved clinical trial or study, as the case may be, under these rules; and

8. In view of above, following are proposed for deliberation & discussion of CSC:

a. Review of reported SAEs.
b. Suspension of the Clinical Trial for further enrolment (after giving an opportunity to PI & CRO), if it is required & deems fit.
c. Further investigation by the IRB, NBC, DSMB & CSC nominated expert team that, the reported SAEs are due to Investigational Medicinal Products (IMPs) or otherwise.

9. The Secretary CSC presented the case before the Committee and the case is discussed as follows:

Discussion;

Following Site PIs & CRO representatives joined the meeting through Zoom and some of Site PIs presented SAEs

i. Dr. Sadia Asim **(Site-PI)**, Director IBBPS, DUHS, Karachi
ii. Dr. Muneeba Ahsan Sayeed **(Site-PI),** Assistant Professor, Department of Infectious Diseases, Sindh infectious Diseases Hospital & Research Center, NIPA, Karachi.
iii. Prof Dr. Ume Sughra **(Site-PI)**; Al-Shifa Research Center, Al-Shifa Trust, Eye Hospital. Rawalpindi.
iv. Dr. Muhammad Ahmad **(Site-PI)**, (Director-CTU) Associate Professor & HOD of Pulmonology and Critical Care, Central Park Teaching Hospital, Lahore.

v. Dr. Mir Abdul Waheed **(Site-PI)**, Medical Director, Consultant & Head of Emergency Medicine, Maroof International Hospital, Islamabad.
vi. Dr. Sajjad Ali **(Site-PI)**, Consultant Internal Medicine and Infectious Diseases, Associate Professor of RMI Peshawar.
vii. Dr. Murtaza & Dr. Sayed Sharib from M/s Metrics Research, Karachi.

- Prof. Dr. Raza Shah, National-PI could not join the meeting
- Prof. Dr. Ume Sughra, Site-PI informed the CSC about another SAEs experienced by a 66 years old female who was enrolled on 14th April, 2023. She explained that on a routine phone call to the subject for suspected Covid screening and dairy card 1 reminder the subject's son reported that subject has passed away due to myocardial infarction.
- Other site PIs introduced them and briefed about the reported SAEs.
- Representatives of CRO informed that a total of 8288 subjects were screened whereas 7092 were randomized and 7012 were vaccinated till 2nd May, 2023. They also informed that all the SAEs has been reviewed by Data & Safety Monitoring Board. As per presentation submitted by the CRO total 963 Adverse events has been observed.
- CSC members showed great concerns on the reported and unreported SAEs and decided as follows:

Decision:

The CSC after detailed discussion and deliberation decided the case as follows:

i. *To suspend the Clinical Trial titled "A Multi-Center, Randomized, Blinded, Placebo-Controlled, Phase-III Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of SARS-COV-2 Bivalent mRNA Vaccine (LVRNA021) as Booster in Participants aged 18 Years and Older Who Completed Primary/1 Booster Dose(s) of SARS-COV-2 Vaccination" for further enrolment.*
ii. *Directed & advised the National PI & CRO:*
    a. *To submit all SAEs whether major or minor along with IRB, DSMB reports and its minutes to the Pharmacy Services Division-DRAP.*
    b. *To submit Post-Vaccination Coagulation Profile (complete), including fibrinogen level of all enrolled subjects.*
    c. *To submit the detailed measures taken regarding management of SAEs/compensation given to subjects.*

The meeting ended with vote of thanks to and from the Chair.