MINUTES OF 39TH MEETING OF THE CLINICAL STUDIES COMMITTEE HELD ON 28th FEBRUARY, 2023.

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The 39th meeting of Clinical Studies Committee was held on 28th February, 2023 in the committee room, Drug Regulatory Authority of Pakistan, G-9/4, Islamabad. The meeting was chaired by Dr. Obaidullah, Director Pharmacy Services. The meeting was started with recitation of the Holy Verses. Following members attended the meeting:

1.	**Prof. Dr. Fazal Subhan.**	Department of Pharmacy, CECOS University of IT & Emerging Sciences,	Member
2.	**Prof. Munawar Alam Ansari.**	Professor of Pharmacology, Dean Faculty of Pharmacy, Liaquat University of	Member
3.	**Dr. Mirza Tasawer Baig.**	Associate Professor in the Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi & Clinical	Member
4.	**Dr. Faiza Bashir**	Nominee of Chairman, Pakistan Health Research Council, Islamabad.	Member
5.	**Mr. Waqas Latif**	Data Analyst/Biostatistician in Quality Enhancement Cell (QEC) at University of	Member
6.	**Ahsan Ul Haq Athar**	Deputy Director-II, Pharmacy Services Division-DRAP.	Secretary/Member

2. **Prof. Dr. Fazal Subhan**, Mr. Waqas Latif & Mr. Shafqat Hussain Danish, Assistant Director (PS) joined the meeting online through zoom link. Mr. Nouman Yousuf, Hafiz Muhammad Jawad & Malik Muhammad Asad assisted the Committee & Secretary in presentation of the agenda.

AGENDA ITEM I:

Subject: **APPLICATION FOR APPROVAL AND REGISTRATION OF CLINICAL TRIAL TITLED "A RANDOMIZED, DOUBLE-BLIND PHYSIOLOGICAL SALINE-CONTROLLED CLINICAL STUDY TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF SARs-CoV-2 VARIANT (BA.4/5) mRNA vaccine (ABO1020) IN HELTHY SUBJECTS 18YEARS AND OLDER WHO HAVE COMPLETED FULL VACCINATION" (F. No.03-33/2023-CT(PS)).**

The case is application from Maj. Gen. Prof. Dr. Aamir Ikram, CNIC No.51401-0924276-9, National Institutes of Health, Islamabad, wherein request has been made for approval of subject Clinical Trial. Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide Slip number. 52496761, dated 26th January, 2023.

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

i. **Sponsor:** Suzhou Abogen Biosciences Co., Ltd.

Brief Summary: The investigational vaccine, SARS-CoV-2 Variant (BA.4/5) mRNA Vaccine (hereafter referred to as ABO1020), in the study is a SARS-CoV-2 messenger ribonucleic acid (mRNA) vaccine developed based on the SARS-CoV-2 mRNA vaccine (AWcorna). Its active ingredients consist of 15 µg of the mRNA encoding for the spike protein (S protein) receptor binding domains (RBD) of the SARS-CoV-2 Omicron sublineages BA 4/5 (BA.4 and BA.5 have identical S protein sequence). It is prepared by encapsulating mRNA with lipid nanoparticles (LNP) delivery system. This Phase 1/3 study includes a Phase 1 part and a Phase 3 part. The Phase 1 part aims to investigate the safety, tolerability and immunogenicity of 2-dose immunization of ABO1020. The Phase 3 study aims to investigate the efficacy, safety, and immunogenicity of 2-dose immunization of ABO1020. The subjects in both Phase I and Phase 3 are ≥18 years old and have completed the full vaccination (subjects with full vaccination is defined as subjects who have previously been fully vaccinated either by 2 or 3 doses of SARS-CoV-2 inactivated vaccine).

Condition or Disease	**Intervention/ Treatment**	**Phase (as per US National Trial Registry).**
Covid 19	Biological: ABO1020Biological: Placebo	Phase 2 Phase 3

ii. Study IMPs required along with justification:

Intervention name	**ABO 1020**	**Physiological Saline**
Manufacturer	Suzhou Abogen Biosciences Co., Ltd	Suzhou Abogen Biosciences Co., Ltd
Specification	15 µg prefilled syringe (0.5ml)	0.5 ml physiological saline
Main ingredients	ABO 1020	BNT162b2
Formulation	IM Injection	IM injection
Appearance	Colorless to slightly opalescent Liquid, free of visible particulates	A colorless, clear liquid
Dose regimen and route of administration	15µg	-----
Storage	2°C – 8°C	2°C – 8°C

iii. Quantity of IMPs required along with justification:

Study Intervention	**Test Drug**	**Comparator**
Intervention Name	ABO 1020	Physiological saline
Dose Formulation	IM Injection	IM Injection
Each Sachet Contains	15µg	0 µg
Quantity to be imported	3000	3000
Total IMPs	6000	
Total subjects to be recruited in Pakistan	0-2000 subjects	

iv. Source of IMP:

v. Number of subjects to be recruited: **15000** participants (Globally)

vi. Anticipated cost of the project: USD 16,00,000 for Pakistan.
USD 800 per subjects

vii. Study design & details:

Study Type	Interventional (Clinical Trial)
Allocation:	Randomized
Intervention Model:	Parallel Assignments
No. of Subjects	0-2000 in Pakistan
Masking:	Triple (Participant, Investigator, Outcomes Assessor)
Primary Purpose	Prevention
Official Title:	A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate the Efficacy, Safety, and Immunogenicity of SARS-CoV-2 Variant (BA.4/5) mRNA Vaccine (**ABO1020**) in Healthy Subjects Aged 18 Years and Older Who Have Completed the Full Vaccination.

3. The study will be carried out at mentioned sites comprising of following as US National Trial Registry;

Site(s)	**Contact**	**Remarks**
Central Hospital, Gujranwala	Salman Athar	**As per Us Trial Registry NIH is not a proposed site for subject study.**
Maroof International Hospital, Islamabad.	Sajjad Naseer	
Rehman Medical Institute, Peshawar	Sajjad Ali	
Akram Medical Complex, Lahore	Javed Akram	
Avicenna Medical College and Hospital, Lahore	Dr. Waheed Ahmed	
The Central Park Teaching Hospital, Lahore.	Dr. Muhammad Ahmad	
National Hospital and Medical Center	Nadia Majeed	
Al- Shifa Trust Eye Hospital, Rawalpindi	Ume Sughra	

Primary & Secondary Objectives

i. To evaluate the safety and tolerability of ABO 1020 within 28 days after each dose **(Primary).**
ii. To evaluate the humoral immunity of ABO 1020 28 days after each dose.
iii. To evaluate the long term safety of ABO 1020 in all subjects.

4. The details of the submitted documents are as under;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Prescribed Fee	Rs. 200,000/- deposited vide Slip number. 52496761, dated 26th January, 2023.
3	Investigator Brochure (s)	Version 1.0 dated 8th July 2022 **Investigator Brochure does not cover the studies carried out with ABO 1020. Updated IB required with Phase I & II studies of ABO 1020.**
4	Final protocol	Attached Protocol # ABO1020-301 Protocol Version PAK 2.0 dated 6th January 2023. **While as per approval in Philippines the approved version is 1.0.**
5	Informed consent and participant information sheet (Urdu to English)	Attached**.**
6	List of participating countries	Philippines, Pakistan, UAE and Indonesia.
7	Phase of trial.	Phase – III

		This study is Phase I & III in multiple countries, only phase III part of study will be conducted and enrollment activities of phase III will be initiated when the safety data of phase-I will be released and analyzed.
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.	***Only phase III part of this study will be conducted the enrollment amount of phase-III subjects will be maximum 2000 in Pakistan. The overall IMPs/ Placebo quantity plan to be imported sites in Pakistan is separate 3000 (with syringe), total 6000.***
9	Sites of the trial	National institute of Health, Islamabad 0-2000 global competitive enrolment.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref.No.4-87/COVID-134/NBC-23/ dated 07 February, 2023.
12	CV's of the Investigators	CV of Maj. Gen. Aamir Ikram is attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	***Not attached.*** ***Instead of GMP certificate issued by Government Authority, The GMP compliance issued by Firm is attached.***
14	Pre-clinical/clinical safety studies.	**Not Attached.**
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.	0-2000 global competitive enrolment.
19	Name of Monitors & Clinical Research Associate	Abdullah Mir Muhammad Salman Tariq NIH, Islamabad.
20	Evidence of registration in country of origin.	**Not registered product.**
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	Approximately 12 months
23	Undertaking on Stamp paper	**Not Attached.**

5. After evaluation following shortcoming/ queries have been observed:

A. Investigator's Brochure (IB):

i. Updated IB required with pre-clinical Phase I/ II clinical & safety studies of ABO 1020 as in submitted IB preclinical & clinical studies of AWcorna, ABO-CoV.617.2 (Delta variant vaccine) and ABO1009-DP (Omicron BA.1 variant vaccine) have been provided rather than ABO-1020 (proposed IMP).

B. Protocol:

i. The subject trial/study is a Multi-Country Trial, so, its protocol should be same for all participating countries. Whereas, a separate Protocol Version PAK 2.0 dated 6th January 2023 is attached for Pakistan only. Its Master Protocol Version 1.0 & 2.0, which got approval in Philippine need to be provided with summary of changes with justification.

ii. As per documents, only phase III trial will be carried out in Pakistan, while attached Pakistan specific Protocol # ABO1020-301, Version PAK 2.0 dated 6th January 2023 is designed for both Phase I & III.

iii. In attached Pakistan specific Protocol # ABO1020-301, Phase-II data is not provided and claimed that Phase-II studies will not be carried out. Justification required for not conducting phase II studies.

C. IRB/ERC & NBC

i. Attached IRB approval is dated 27th December 2022 & protocol version PAK 2.0 is approved on dated 6th January 2023 and signed by PI on 11.01.2023. It needs to be clarified that, how can a protocol can be approved before its finalization?

ii. IRB approval is without following information:
   a. Phase of trial.
   b. Documents reviewed & approved by IRB.

iii. Phase of trial is not mentioned in NBC approval granted vide Ref.No.4-87/COVID-134/NBC-23/ dated 07 February, 2023.

D. Other:

i. As per US Trial Registry Identifier No. NCT05636319, the trial is enlisted for Phase-II & III and National Institute of Health, Islamabad is not mentioned there as a site for the trial in Pakistan.

ii. As per Wuxu data Trial Registry Identifier No. NCT05636319, the trial is enlisted for Phase-I and II to be carried out in U.A.E. & trial status is *"Not yet recruiting"*, justification is required that if Phase-I/II is not completed yet, so, why its Phase-III need to be conducted.

iii. Details regarding Laboratory/ tests required along with Material Transfer agreement and SOP.

iv. GMP certificate of manufacturer of Jiangsu GenScript ProBio Biotechnology Co., and Suzhou Abogen Biosciences Co., Ltd. is required.

v. CoPP/ Free Sale Certificate, Registration Certificate (if applicable) of Physiological Saline being IMP is required

vi. Justification for the quantities of IMPs to be imported is required.
vii. Undertaking on Stamp Paper is not attached.

6. The shortcomings were communicated vide this office letter 03-33/2023 dated 15 February, 2023. The applicant has submitted their reply dated 27th February 2023 which has been evaluated as follows;

	DRAP Queries	**PI Response**
1	Updated IB required with pre-clinical Phase I/II clinical & safety studies of ABO1020 as in submitted IB Pre-clinical & clinical studies of AWcorna, ABO-CoV.617.2(Delta variant vaccine) and ABO1009-DP (Omicron BA.1 variant vaccine) have been provided rather than ABO1020 (proposed IMP).	Clinical data for Phase 1 study has been submitted and will be incorporated into IB amendment in annually review/ update. AWcorna, ABO-CoV.617.2, ABO1009-DP and ABO1020 are developed using the same mRNA platform. AWcorna is the prototype vaccine, ABO-CoV.617.2 and ABOL009-DP and ABO1020 are the modified vaccines, the clinical safety profile of ABO1020 could be inferred from ABO-CoV.517.2 and ABO1009-DP, which showed a good Safety profile.
1	The subject trial/study is a Multi-Country Trial, so, its protocol should be same for all participating countries. Whereas, a separate Protocol Version PAK 2.0 dated 6th January 2023 is attached for Pakistan only. Its Master Protocol Version 1.0 & 2.0, which got approval in Philippine need to be provided with summary of changes with justification.	The PAK specific protocol has no substantial change with the Master protocol, only revised the placebo to physiological saline, along strictly keep consistence with Master protocol V2.0 in study design, study flowchart and other content. Protocol main change summary from 1.0 to 2.O, refer to protocol for more details; 1. Removed the tests of anti-SARSCoV-2 (Omicron variant) S-RBD specific IgG antibody levels and pseudo virus neutralizing antibody titers. 2.Updated the Endpoint case definition per relevant guidelines. 3. Sample size of phase 3 part is revised from 6000 to 15000 and added a sentence to describe the criteria to stop enrollment, as Statistical assumption parameters were changed upon the prediction of the epidemic. 4. To simplify the visit procedure and optimize the study resource on the efficacy follow ups, Removed blood test items (blood routine, blood biochemistry, urinalysis, and coagulation function, Serology test of selected infectious diseases) at screening visit (V1) in phase 3 part. Remove on-site visits V2 (14 days after first dose) and V4 (14 days after second dose) and corresponding tests (Diary cards, RT-PCR test and AE/Concomitant Medication). The frequency of long term of safety follow-up reduced to 3 times in total after V2 by phone or e-mail. All subjects will have remote Visit (via telephone/Email) on V2+ 90, 180, 350 days (±15 days).
2	As per documents, only phase III trial will be carried out in Pakistan, while attached Pakistan specific Protocol # ABO1020-301, Version PAK 2.0 dated 6th January 2023 is designed or both Phase I & III.	As a multi-Country Trial, the protocol main content should be consistent in all countries as question 1 mentioned, so even in Pakistan specific protocol, the phase I part is included as well.

3	In attached Pakistan specific Protocol # ABO1020-301, Phase-II data is not provided and claimed that Phase-II studies will not be carried out. Justification required for not conducting phase II studies.	According to the guideline, <Technical Guideline for Clinical Studies of Preventive Vaccines of Novel Coronavirus (For Trial implementation)>, sequentially trials in adults and older adults and phase 1 and Phase 2 trials can be fast-tracked in response to the critical situation of the COVID-19 pandemic. Moreover, Phase-II clinical trials should consider adequate exploration of immune dose and immune program (dos, interval). For the investigational vaccine in the study, the dose and interval had been determined by the previous vaccines using the same mRNA technology platform via clinical trials. Therefore, there is no Phase 2 part of the study.
1	Attached IRB approval is dated 27th December 2022 & protocol version PAK 2.0 is approved on dated 6th January 2023 and signed by PI on 11.01.2023. It needs to be clarified that, how can a protocol can be approved before its finalization?	New IRB Approval attached.
2	IRB approval is without following information: a. Phase of trial. b. Documents reviewed & approved by IRB.	New IRB Approval attached.
3	Phase of trial is not mentioned in NBC approval granted vide Ref.No.4-87/COVID-134/NBC-23/ dated 07 February, 2023.	New IRB Approval attached.
1	As per US Trial Registry Identifier No. NCT05636319, the trial is enlisted for Phase-II & III and National Institute of Health, Islamabad is not mentioned there as a site for the trial in Pakistan.	The study overall status will be updated by sponsor based on study process, for special country/site status, the latest information will be updated no later than FSI (First subject enrollment)
2	As per Wuxu data Trial Registry Identifier No. NCT05636319, the trial is enlisted for Phase-I and II to be carried out in U.A.E. & trial status is *"Not yet recruiting"*, justification is required that if Phase-I/II is not completed yet, so, why its Phase-III need to be conducted.	The trial status was updated to "Recruiting" on Feb 9,2023.
3	Details regarding Laboratory/ tests required along with Material Transfer agreement and SOP.	Sponsor prefer to use site own lab to conduct all study lab test, which is assumed a qualified lab in PKA and its SOP/procedure will be strictly followed. Meanwhile, Sponsor have no intention to use global central lab to handle any test in PKA.
4	GMP certificate of manufacturer of Jiangsu GenScript ProBio Biotechnology Co., and Suzhou	Drug Manufacturing Certificate of Suzhou Abogen Biosciences is enclosed.

	Abogen Biosciences Co., Ltd. is required.	
5	CoPP/ Free Sale Certificate, Registration Certificate (if applicable) of Physiological Saline being IMP is required	Not Applicable
6	Justification for the quantities of IMPs to be imported is required.	Considering only phase III part of this study will be conducted, and the enrolment amount of phase III subjects will be maximum 2,000 in Pakistan, the overall IMP/placebo quantity plan to be imported sites in Pakistan is separate 3,000 (with syringe), total 5,000. 2,000 will be the excess quantity and take into account the IMP damage or temperature excursion which causes some IMP will be not available to use.
7	Undertaking on Stamp Paper is not attached	Attached

Discussion:

The case was placed before the CSC and was discussed at length. On the behalf of Sponsor following representatives joined the meeting through Zoom:

Mr. Omar Malik	*Lynn Zhou*	*Dandan Yu*
Helen He	*Jason Yuan*	*Hongxia Zheng*

2. The CSC discussed the case in detail and raised different queries regarding safety and efficacy data of Phase-I clinical trial, Pakistan specific protocol, GMP certificate and others.

3. Representative of the NBC informed that, the NBC is not granting approvals to Placebo-Controlled trials for the Primary COVID-19 Vaccine. Previously, many of COVID-19 booster dose vaccine trials has been granted with placebo. It is not clear that, why the word Placebo has been replaced with Physiological Saline.

4. Miss Lynn Zhou apprised CSC that data of Phase-I of Clinical Trial is not available right now and will be shared as soon as it becomes available. Another representative M/s Abbogen informed that currently GMP certificate not available as currently China regulatory authority is not issuing GMP certificate but various inspections during NDA approval were conducted. Further, she informed that they have valid DML from China National Medical Products Administration.

5. Miss Dandan Yu informed that the actual study design has also Phase-II studies. She informed that in UAE, country specific Protocol has Phase-I/II/III clinical studies. She suggested that we will submit a revived protocol with title as phase-II and phase-III studies. Representatives also informed the CSC that Phase-I safety data after seven days of 1st dose (IMP) has been submitted while data regarding 2nd dose (at 28th day) is yet to be finalized and will be submitted accordingly.

Decision:

CSC after detailed discussion and deliberation decided to defer the Clinical Trial titled, "*A Randomized, Double-Blind Physiological Saline-Controlled Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of SARS-COV-2 Variant (BA.4/5) mRNA Vaccine (ABO1020) in Healthy Subjects 18 Years and Older Who Have Completed Full Vaccination" in the light of proposal of representative of M/s Abbogen regarding submission of revised protocol designed for Phase-II and Phase-III. Further, CSC decided to direct the applicant to submit following documents;*

i. *Safety and Efficacy data with Two doses along with Data Safety & Monitoring Committee (DSMC) report after completion of Phase-I studies.*
ii. *Valid DML issued by China NMPA/FDA.*

iii. Any other document required under revised protocol including approval of relevant IRB and NBC.

AGENDA ITEM II:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED, "A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATE THE EFFECT OF, Bi-26 (STAIN OF BIFIDOBACTERIUM LONGUM, B. INFANTIS) SUPLEMENTATION VS PLACEBO ON WEIGHT GAIN ON UNDER WEIGHT INFANTS", AL-SHIFA TRUST EYE HOSPITAL, RAWALPINDI. F. No.03-31/2023-DD (PS)

Application received from Prof. Dr. Ume Sughra, CNIC No.37405-0579220-0, Director Research, Al-Shifa Trust Eye Hospital, Jhelum road, Rawalpindi, wherein request has been made for approval of subject Clinical Trial. Application is on prescribed Form-II (printed on hospital letter head), along with a fee of Rs. 200,000/- deposited vide Slip number. 784900120783, dated 27th December, 2022.

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

i. **Sponsor:** Bill & Melinda Gates Medical Research Institute.

ii. **Brief Summary:** The Bi-26 supplement is presented as a lyophilized powder. A single dose of supplement will be re-suspended and administered to the participant each day for 28 days. Once a day, the mother mixes the powder with approximately 3 mL to 5 mL of breastmilk and administers to the infant orally using a feeding syringe. In keeping with current World Health Organization (WHO) recommendation that children are exclusively breast-fed for the first 6 months of life [WHO 2022], breastmilk is preferred for mixing the supplement. If the mother is unable to express breastmilk, the powder may be mixed in approximately 3 mL to 5 mL of water. While a total of 7 doses of Bi-26 supplement are to be administered per week, one each day, 9 doses will be provided each week to allow for an additional 2 doses, if needed, for repeat dose administration in the event of vomiting, or unexpected events which may render a dose unusable (e.g., spillage or otherwise compromised). Any additional dose/s not administered will be collected by study staff at the following visit. Doses will either 1) be delivered to the mother by study staff, or 2) stored by staff, at the local health center to be picked up from the health center. Study activities are assigned to the mother of the infant participant because the preferred method of reconstitution of the study intervention is in breastmilk. However, other caretakers may perform certain study activities (e.g., picking up the study doses, assisting in completion of the feeding diary, etc.).

iii. Two treatment groups, shown below, will be enrolled in parallel.

Intervention	**Duration of Study Intervention**	**No. of Participant Randomized.**
Bi-26	28	198
Placebo	28	198

iv. Study IMPs required along with justification:

Intervention name	**Bi-26**	**Placebo**
Manufacturer	Danisco USA 3322-3329 Agriculture Drive, Madison, Wisconsin, 52716, USA.	Danisco USA 3322-3329 Agriculture Drive, Madison, Wisconsin, 52716, USA.
Specification	Each Sachet contains 1gm (I dose) 9 doses per carton	Each Sachet contains 1gm (I dose) 9 doses per carton
Main ingredients	*Bifidobacterium infantis (*Bi-26 stain*)*	Potato malto-dextrin
Formulation	Sachet	Sachet
Appearance	White to light yellow powder	White to light yellow powder
Dose regimen and route of administration	First Day: Single dose sachet containing 1 gm /day for 28 days.	First Day: Single dose sachet containing 1 gm /day for 28 days.
Storage	Room Temperature (2-8°C)	Room temperature (2-8°C)
Batch number and	1104277614	1104277612

expiration date	17.10.2024	11.10.2024

v. Quantity of IMPs required along with justification:

Study Intervention	**Test Drug**	**Placebo**
Intervention Name	Bi-26	Placebo
Dose Formulation	Powder	Powder
Each Sachet Contains	1 gm (single dose)	1 gm (single dose)
Quantity to be imported	10,890 sachet.	
Total box to be imported	1220 cartons	
Total subjects to be recruited in Pakistan	200 (226 including drop out)	

- **Source of Investigational Medical Products (IMPs):** USA.

vi. Number of subjects to be recruited: 3966 Subjects (Globally)

vii. Anticipated cost of the project: USD 593,600 for 200 subjects

viii. Study design & details:

Study Type	Interventional (Clinical Trial)
Allocation:	Randomized
Intervention Model:	Parallel Assignments
Masking:	Double-Blind (The Gates MRI medical monitors, Study Monitors, any other gates MRI and CRO personal who are regularly in contact with study sites)
Official Title:	A PHASE IIII RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATE THE EFFECT OF, Bi-26 (STAIN OF BIFIDOBACTERIUM LONGUM, B. INFANTIS) SUPLEMENTATION VS PLACEBO ON WEIGHT GAIN ON UNDER WEIGHT INFANTS.

3. The study will be carried out at mentioned sites comprising of following primary objective(s);

Site(s)	**PI**	**Specialty**	**Phase of trial**	**Remarks**
Agha Khan University, Karachi	Dr. Sonia Qureshi (Site-PI)	Pediatric and Child Health	Phase- III	---
The Central Park Teaching Hospital, Lahore.	Dr. Muhammad Fakhar Ul Zaman (Site-PI)	Not mentioned	Phase-III	
Shifa International Hospital, Islamabad.	Dr. Munir Iqbal Malik (Site-Pi)	Consultant Pediatrician	Phase-III	
Avicenna Medical College and Hospital, Lahore	Dr. Aneela Zareen (Site-Pi)	Pediatrician & Neonatology	Phase-III	
Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi.	Dr. Ume Sughra (National PI)	Epidemiologist	Phase-III	
Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad.	Prof. Dr. Maqbool Hussain (site-Pi)	Pediatric Medicine	Phase-III	
Maroof International Hospital, Islamabad.	Dr. Mahmood Jamal (site-PI)	Pediatric & Neonatology	Phase-III	

Primary & Secondary Objectives

i. To evaluate the change in weight (standardized for age) of infants receiving Bi-26. **(Primary)**

ii. To evaluate the change in weight of infants receiving Bi-26 (key secondary).

4. The details of the submitted documents are as under;

S. No.	**Document**	**Remarks**
1	Application on prescribed Form-II	Attached. **Printed on letter head of Al Shifa Trust.**
2	Prescribed Fee	Rs. 200,000/- deposited vide Slip number. 784900120783, dated 27th December, 2022.

3	Investigator Brochure (s) Investigator Brochure Addendum	Edition 3.0 Version 6 dated 31 March 2022 Addendum 1 version 2 31 May 2022
4	Final protocol	Attached Protocol: gates MRI-MNK01-301 Protocol Version 4.0 dated 12 September 2022. **Protocol not signed by PI or sponsor.**
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Tanzania, Kenya, Bangladesh and Pakistan.
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.	Bi-26 + placebo = 1220cartons. Each carton contains 9 single dose sachet of Bi-26 or placebo Total subjects to be recruited in Pakistan =200 Subjects including drop out = 226 Sachet required for 226 subjects = 904 (2 sachets extra per week) Loss due to temperature excursion = 45 carton Loss at site = 45 carton Extra overage = 316 carton The required IMP for trial is 5600 doses Extra doses = 5530. **Firm needs to develop SOPs for logistic, established supply chain handling and storage of IMPs.**
9	Sites of the trial	Agha Khan University, Karachi The Central Park Teaching Hospital, Lahore. Shifa International Hospital, Islamabad. Avicenna Medical College and Hospital, Lahore Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi. Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad. Maroof International Hospital, Islamabad
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Agha Khan University, Karachi. The Central Park Teaching Hospital, Lahore (257-259). Shifa International Hospital, Islamabad (262-264). Avicenna Medical College and Hospital, Lahore (268-270) Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi (253-256). Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad (260-261) Maroof International Hospital, Islamabad (265-267)
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref # 4-87/NBC-896/23/1102, dated 27th January, 2023.
12	CV's of the Investigators	CVs of following (site-PI & national-PI) are attached. Dr. Sonia Qureshi (Site-PI) at Agha Khan University, Karachi (178-204) Dr. Muhammad Fakhar Ul Zaman (Site-PI) The Central Park Teaching Hospital, Lahore (216-218).

		Dr. Munir Iqbal Malik (Site-Pi) Shifa International Hospital, Islamabad (209-215). Dr. Aneela Zareen (Site-Pi) Avicenna Medical College and Hospital, Lahore (222-227). Dr. Ume Sughra (National PI) Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi (235-249). Prof. Dr. Maqbool Hussain (Site-Pi) Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad (219-221). Dr. Mahmood Jamal (site-PI) at Maroof International Hospital, Islamabad (205-208).
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Manufacturer of Drug is Danisco, USA Packaging by Fisher Clinical services
14	Pre-clinical/clinical safety studies.	Given in investigator Brochure
15	Summary of Protocol	Attached
16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting Form	Adverse Event Summary Form attached.
18	No of patients to be enrolled in each center.	Agha Khan University, Karachi **(40).** The Central Park Teaching Hospital, Lahore **(30)** Shifa International Hospital, Islamabad **(20)**. Avicenna Medical College and Hospital, Lahore **(30).** Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi **(40)**. Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad **(20)**. Maroof International Hospital, Islamabad **(20).**
19	Name of Monitors & Clinical Research Associate	**Karachi:** Sadia Hashmi, Sadia Altaf **Islamabad:** Asjid Ali Arshad, Sidra Rashid, Naveed Akbar. **Lahore:** Mahir Ahmad, Hasina Sarwar, Saad Asadullah, Muhammad Asif Mehmood.
20	Evidence of registration in country of origin.	**Product is registered as Trademark but evidence of registration not attached.**
21	Copy of registration letter (if registered in Pakistan)	**Not applicable/ Not Registered in Pakistan.**
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	Approximately 1 year from start of recruitment until close out (March 2022 to January 2024)
23	Undertaking on Stamp paper	Attached.

5. The GMP certificate of M/s Danisco USA Inc. has been issued by NSF International, USA and GMP certificate of Fisher Clinical Services Inc., 7554 Schantz Road, Allentown, PA, 18106, United States by Medical Product Agency (LAKEMEDELSVERKET), Sweden. Applicant has shared master version of ICF (Urdu and English) and electronically signed protocol.

6. Technical documents (Investigator's Brochure & Trial Protocol) has been already shared with CSC members.

7. The case was placed before the Committee. Mr. Syed Munawar, representative of Sponsor/CRO & Dr. Umme Sughra, PI of the trial also joined the meeting & responded queries raised by the CSC members.

Decision: -

The CSC after detailed discussion decided to defer the Clinical Trial titled, "A Phase-III Randomized, Double-Blind, Placebo-Controlled Study Evaluate the Effect of, Bi-26 (Strain of Bifidobacterium Longum, B. Infantis) Supplementation Vs Placebo on Weight Gain on Under Weight Infants" for further deliberation regarding submitted safety and efficacy studies.

AGENDA ITEM III:

A PHASE III STUDY TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF PTX-COVID19-B ADMINISTERED AS BOOSTER VACCINE IN PREVIOUSLY VACCINATED ADULTS AGED 18 YEARS AND OLDER. F. No.03-32/2023-DD (PS).

Application was submitted by Prof. Dr. Muhammad Ahmad, CNIC No.31304-4798820-7, Director Clinical Trial Unit, Central Park Teaching Hospital, Lahore, wherein request has been made for approval of subject Clinical Trial. Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide Slip number. 9560710868, dated 29th December, 2022.

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

i. **Sponsor:** Everest Medicines (Singapore) Pte. Ltd.

Brief Summary: The purpose of this clinical trial is to Evaluate the Safety and Immunogenicity of PTX-COVID19-B Administered as Booster Vaccination in Previously Vaccinated Adults Aged 18 Years and Older.

3. This study is seeking participants who are:

Adult males and females 18 years of age or older; In efficacy cohort: Subjects who were previously vaccinated with 2 doses of Comirnaty® administered at least 3 months prior to the booster dose.

All participants in this efficacy cohort will receive 1 of the 2 study vaccines: PTX-COVID19-B or Comirnaty®.

All participants in efficacy cohort will receive a single 40 microgram dose PTX-COVID19-B of the study vaccine or one dose of Comirnaty® at the first study clinic and will return to the study clinic 6 more times. At each clinic visit, a blood sample will be taken. They study is about 6 months long for each participant.

In safety cohort: Subjects who have previously received any primary series approved by WHO Emergency Use Authorization at least 3 months prior to enrollment or subjects who have already received one authorized booster vaccination and planned to receive PTX-COVID19-B as the 4th shot will be enrolled.

All participants in this safety cohort will receive 1 dose vaccines: PTX-COVID19-B.

All participants in safety cohort will receive a single 40 microgram dose of the study vaccine at the first study clinic and will return to the study clinic 5 more times. At each clinic visit, a blood sample will be taken. They study is about 6 months long for each participant.

Condition or Disease	**Intervention/ Treatment**	**Phase .**

SARS-CoV-2 Infection	Biological: PTX-COVID19-B Biological: Comirnaty®	Phase 3

ii. Study IMPs required along with justification:

Intervention name	**PTX-COVID19-B**	**Comparator**
Manufacturer	Emergent BioSolutions, 155 Innovation Drive, Winnipeg, MB Canada.	Biotech Manufacturing GmbH., Kupferbergterrasse 17-19 Oberstadt, Mainz, Rhineland-Palatinate, 55116.
Specification	Sterile mRNA-lipid nanoparticle (mRNA-LNP) 0.2mg/mL, 2.4mL filled in a 6mL vial **With 3.6ml diluent** **10 doses per vial**	30µg BNT162b2 per dose (0.3mL) Diluent 1.8ml **6 doses per vial**
Main ingredients	mRNA-lipid nanoparticle (mRNA-LNP)	BNT162b2
Formulation	IM Injection	IM injection
Appearance	Diluted vaccine transparent, slightly off white suspension with no visible particulate.	White to off white preservative free frozen suspension.
Dose regimen and route of administration	40µg, IM	30µg, IM
Storage	Long term storage and Transportation -20°C – -80°C Frozen and unopened vaccine vials -20°C – -80°C Unopened and thawed vaccine vials 2°C – 8°C (One Month) Opened/diluted for injection vaccine vials 2°C – 8°C (Maximum 6 Hrs.) During vaccine administration (filling of syringes) 15°C - 25°C (Maximum one (1) hour)	*Frozen vial* 9 months when stored at -90 °C to -60 °C. Within the 9-month shelf-life unopened vials may be stored and transported at -25 °C to -15 °C for a single period of up to 2 weeks and can be returned to -90 °C to -60 °C. When stored frozen at -90 °C to -60 °C, 195-vial packs of the vaccine can be thawed at 2 °C to 8 °C for 3 hours or individual vials can be thawed at room temperature (up to 30 °C) for 30 minutes. *Thawed vial* 1 month at 2 °C to 8 °C within the 9-month shelf life. Within the 1-month shelf life at 2 °C to 8 °C, up to 12 hours may be used for transportation. Prior to use, the unopened vial can be stored for up to 2 hours at temperatures up to 30 °C.

iii. Quantity of IMPs required along with justification:

Study Intervention	**Test Drug**	**Comparator**
Intervention Name	Sterile mRNA-lipid nanoparticle (mRNA-LNP) 0.2mg/mL, 2.4mL filled in a 6mL vial	30µg BNT162b2 per dose (0.3mL)(after dilution of DP with sterile isotonic Sodium Chloride solution (0.9% NaCl))
Dose Formulation	IM Injection	IM Injection
Each vial Contains	40µg	30µg
Quantity to be imported	152 vials	32 Vials
Lab kits		
Total subjects to be recruited in Pakistan	660 +150 = 810	

iv. Source of IMP:

v. Number of subjects to be recruited: 3800 participants (Globally)

vi. Anticipated cost of the project: USD 13,35,840 for 660 subjects
USD 387,000 for 150 subjects

vii. Study design & details:

Study Type	Interventional (Clinical Trial)
Allocation:	Randomized
Intervention Model:	Parallel Assignments
No. of Subjects	810 in Pakistan
Masking:	Triple (Participant, Care Provider, Investigator)
Primary Purpose	Prevention
Official Title:	A Phase III Study to Evaluate the Safety and Immunogenicity of PTX-COVID19-B Administered as Booster Vaccination in Previously Vaccinated Adults Aged 18 Years and Older

4. The study will be carried out at mentioned sites comprising of following.);

Site(s)	PI	Specialty	Phase of trial	Remarks
Agha Khan University, Karachi	Dr. Nosheen Nasir (Site-PI)	Infectious disease	Phase- III	---
The Central Park Teaching Hospital, Lahore.	Dr. Muhammad Ahmad (National-PI)	Pulmonology & ICU	Phase-III	
Shifa International Hospital, Islamabad.	Dr. Ejaz Ahmad Khan (Site-Pi)	Pediatric & Infectious Diseases	Phase-III	
Avicenna Medical College and Hospital, Lahore	Dr. Waheed Ahmed (Site-Pi)	Professor of Medicine	Phase-III	

Primary & Secondary Objectives

iii. To demonstrate that the immune response of a single booster dose of PTX-COVID19-B is non inferior to that of Comirnaty® at day 15 **(Primary)**
iv. To describe the immune response of single booster dose of PTX-COVID19-B in efficacy cohort.
v. To assess the immunogenicity of PTX-COVID19-B and Comirnaty® against variant of concern (VOC) in subjects 18 years of age and older.
vi. To assess the safety of PTX-COVID19-B in efficacy cohort.
vii. To assess the efficacy of PTX-COVID19-B and Comirnaty® in the prevention of Covid-19.
viii. To assess the safety of booster vaccination of PTX-COVID19-B in safety cohort.

5. The details of the submitted documents are as under;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached. **Printed on letter head of Central park teaching Hospital, Lahore.**
2	Prescribed Fee	Rs. 200,000/- deposited vide Slip number. 9560710868, dated 29th December, 2022.
3	Investigator Brochure (s)	Version 7 dated 8th November 2022
4	Final protocol	Attached Protocol # COVI-EM-002 Protocol Version 1.0 dated 29th July, 2022.
5	Informed consent and participant information sheet (Urdu to English)	Attached**.**
6	List of participating countries	Philippines, Pakistan, Thailand and Indonesia.
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.	PTX-COVID19-B 152 vials with diluent. Comirnaty® 32 vials PTX-COVID19-B vial contains 10 doses (1520 doses) for 735 subjects. Comirnaty® vial contains 6 doses (192) for 75 subjects. 100% extra doses.
9	Sites of the trial	Agha Khan University, Karachi The Central Park Teaching Hospital, Lahore. Shifa International Hospital, Islamabad. Avicenna Medical College and Hospital, Lahore
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Agha Khan University, Karachi. **(310-311).** The Central Park Teaching Hospital, Lahore **(316-317).** Shifa International Hospital, Islamabad (**262-264).** Avicenna Medical College and Hospital, Lahore **(314-315).**
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref.No.4-87/NBC-128/22/847 dated 26 December 2022.
12	CV's of the Investigators	CVs of following (site-PI & national-PI) are attached. Dr. Nosheen Nasir (Site-PI) at Agha Khan University, Karachi (270-282) Dr. Muhammad Ahmad (National-PI) The Central Park Teaching Hospital, Lahore (266-269). Dr. Ejaz Ahmad Khan (Site-Pi) Shifa International Hospital, Islamabad (283-303. Dr. Waheed Ahmed (Site-Pi) Avicenna Medical College and Hospital, Lahore (304-309).
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP certificate of Biotech Manufacturing GmbH attached (322-323) **CoPP or Free Sale Certificate of Pfizer not attached.** **Good manufacturing Practice statement of Emergent BioSolution Canada is attached instead of GMP certificate.** **Emergent BioSolutions Canada Inc. Winniping site manufacture, packages and test vaccine for clinical purposes at this time and does not currently manufacture, package or test any commercial vaccine products (348)**
14	Pre-clinical/clinical safety studies.	Attached.
15	Summary of Protocol	Attached
16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting Form	Adverse Event Summary Form attached.
18	No of patients to be enrolled in each center.	Agha Khan University, Karachi **(199).** The Central Park Teaching Hospital, Lahore **(214)** Shifa International Hospital, Islamabad **(122)**. Avicenna Medical College and Hospital, Lahore **(275).**
19	Name of Monitors & Clinical Research Associate	**Karachi:** Sadia Hashmi, Ayesha Javed, Sadia Altaf **Islamabad:** Asjid Ali Arshad, Sidra Rashid, Naveed Akbar.

		Lahore: Mahir Ahmad, Hasina Sarwar, Saad Asadullah, Muhammad Asif Mehmood.
20	Evidence of registration in country of origin.	**Not provided**
21	Copy of registration letter (if registered in Pakistan)	**Not applicable** **Pfizer has EUA in Pakistan.**
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	Beginning of January 2023 to 18th December 2023.
23	Undertaking on Stamp paper	Attached.

6. In the light of above, it is submitted that Good Manufacturing Practice statement of Emergent BioSolution Canada is attached instead of GMP certificate. Emergent BioSolutions Canada Inc. Winniping site manufacture, packages and test vaccine for clinical purposes at this time and does not currently manufacture, package or test any commercial vaccine products.

Phase I Clinical Study

A Phase I first-in-human, observer-blinded, randomized, placebo-controlled, ascending dose study in healthy seronegative adults aged 18 to 64 years was performed in Canada with the objective of evaluating the safety, tolerability, and immunogenicity of 16, 40 and 100μg PTXCOVID19- B administered as 2 vaccinations 4 weeks apart (Days 1 and 28), of the 60 randomized subjects (15 active and 5 Placebo in each dose cohort), a total of 45 subjects received at least one dose of COVID19-B vaccine. All subjects in the 16 μg and 100 μg dose groups received both doses and 14/15 subjects received both doses of 40 μg. The 12-month follow-up in this study is complete.

Taken together, the safety, tolerability, and immunogenicity of the 40μg supports the selection of this dose for evaluation in Phase II clinical trials. Taken together, the safety, tolerability, and immunogenicity of the 40μg supports the selection of this dose for evaluation in Phase 2 clinical trials.

Phase II Clinical Study

Sponsor has completed dosing and Day 42 follow up in a Phase II primary vaccination clinical study (PRO-CL-002). This study, which is being conducted in Canada and South Africa, is a randomized, double-dummy, observer-blind, study to evaluate the safety, tolerability, and immunogenicity of 40 μg PTX-COVID19-B compared to Pfizer-BioNTech COVID-19 vaccine (Comirnaty®) in healthy seronegative adults aged 18 to 64 years. Subjects were randomly assigned in a 2:1 ratio to receive two doses of either PTX-COVID19-B vaccine (n=350) or Comirnaty® (n=175).

Preliminary testing for cellular immunity via ELISpot assay on 15 subjects vaccinated with 40 μg of PTX-COVID19-B in the open label portion of the study indicates a predominant IFN-γ production by Day 42, which indicates a favorable Th1 response. Assessment of the immunogenicity response is pending data analysis.

7. The case was presented before the Committee. Mr. Munawar, Sponsor/CRO (IQVIA) representative joined the meeting through Zoom & appraised the Committee that, targeted enrolment has been completed from Philippine & now Sponsor has terminated the trial in Pakistan.

Decision:

The CSC after detailed discussion acceded to the request of the applicant to withdraw the trial titled, "A Phase III Study to Evaluate the Safety and Immunogenicity of PTX-COVID-19-B Administered as Booster Vaccine in Previously Vaccinated Adults aged 18 years and older"

AGENDA ITEM IV:

APPLICATION FOR PPROVAL OF 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)

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	IRB approval of following CTS are attached:

	committee i.e. names and designation of members.	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***

AGENDA ITEM V:

APPLICATION FOR RENEWAL OF LICENSE TO ACT AS CLINICAL TRIAL SITE FROM SHAUKAT KHANUM MEMORIAL CANCER HOSPITAL AND RESEARCH CENTRE LAHORE (15-12/2019 DD (PS)).

The case is an application from Dr. Farah Asif, Clinical Research Administrator, SKMCH&RC, Lahore wherein he has enclosed application on Form-III signed by Dr. Muhammad Aasim Yusuf for renewal of licence to act as clinical trial site. The application is on Form-III of the Bio-Study Rules 2017 with fee of Rs. 100,000/- submitted vide slip number 6737083351.

2. It is submitted that M/s Shaukat Khanum Memorial Cancer Hospital & Research Centre, Lahore was licensed (CTS-0004) to act as Clinical trial site situated 7-A, Khayaban-e-Firdousi, block R 3 M.A. Johar Town, Lahore. They have submitted application for renewal of licence that has been evaluated according pre- requisites as mentioned in Form-I of the Bio-Study Rules 2017, and as following are observations:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-III of The Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	Fee of Rs. 100,000/- submitted vide slip number 6737083351 dated 24.10.2022
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	Regular License issued by Punjab Healthcare Commission, List of members of Board of Governors, Memorandum of Association and Rules and Regulations of the Shaukat Khanum Memorial Trust and Authority letter are attached.
4	Details of premises including layout plan of the site.	Copy of layout plan attached.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Attached
6	Names and qualifications of management.	CVs of Dr. Muhammad Aasim Yusuf, Dr. Faisal Sultan and Asif Loya are attached. List of members of Board of Governors, Memorandum of Association and Rules and Regulations of the Shaukat Khanum Memorial Trust attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Attached
8	Undertaking on stamp paper	Attached.

3. The application has been submitted for renewal of license to act as clinical trial site for Phase II, III & IV on prescribed Form-III along with relevant documents. It is proposed that panel may be constituted for inspection of CTU situated at M/s Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore.

Submitted please.

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The CSC in its 38th meeting held on 8th February 2023, after detail discussion and deliberation decided as follows:

a. ***to delegate its power sunder rule 13(9) of the Bio-Study Rules to the Chairman CSC to constitute panel for the inspection of Contract Research Organization (CRO),*** *Bio analytical Laboratory, Clinical Trial Site, BA/BE Centers, inspection during or after completion of study/ trial and destruction of Investigational Medical Products (IMPs) or Investigational Medical Devices (IMDs) or any other required under rule 8 (13), rule 11 and rule 13(4)(c) or any other rule/ sub-rule of the Bio-Study Rule 2017 to avoid any delay in processing of the application. The panel will submit the inspection report to the Division of Pharmacy Services, DRAP for consideration of for decision.*
b. *The CSC delegated the powers to the Chairman CSC to co-opt member under rule 13 (1)(j). The co-opted shall be subject related expert person having vast experience in relevant field for advice on any particular matter under consideration. The report generated by the co-opted member for therapeutic goods or any other specific matter will be placed before the CSC and such member will also attend and brief on that matter in CSC meeting (if required).*
c. *Advised Pharmacy Services Division to prepare post trial variation list for review and consideration by CSC.*

Accordingly, following panel was constituted;

a. Dr. Noor Muhammad Shah, Director, Division of Controlled Drugs, DRAP, Islamabad.
b. Prof. Dr. Jaida Manzoor, Head of Department of Paeds Endocrinology, Children Hospital & Institute of Child Health (CH & ICH), Lahore.
c. Mr. Ahsan-Ul-Haq Athar, Deputy Director (PS), DRAP, Islamabad **(coordinator).**

The panel conducted the inspection on 24.02.2023 as per check list with following remarks.

"Keeping in view the research center, IMPs storage & dispensing, research expertise & experience, hazardous material & waste management plan, emergency & critical care access, rapid response team (code blue team) manages medical emergencies, integrated medical record/ hospital information system, research related trainings, IMP cycle management from receipt to its final incineration, document retention and archival, The panel recommends the CTS situated at Shaukat Khanum Memorial Hospital and Research Center for renewal of License (CTS 004) for phase II, III and IV. The PK/PD studies will be outsourced/ performed at laboratories designated by the sponsor, if such studies are required during the clinical trial especially for phase II."

Recommended for approval for renewal of license.

Decision:

The CSC in pursuance to the recommendations of the inspection panel & in the light of discussion/deliberations unanimously decided to renew the licence of M/s Shaukat Khanum Memorial Cancer Hospital and Research Centre, Lahore to act as Clinical Trial Site for Phase-II, III & IV Clinical Trials as per their initial application. The PK/PD studies will be outsourced/ performed at laboratories designated by the sponsor, if such studies are required during the clinical trial especially for phase II.

AGENDA ITEM VI:

ADDITION OF A SITE IN ALREADY APPROVED CLINICAL TRIAL TITLED "A RANDOMIZED, DOUBLE-BLIND CLINICAL STUDY OF THE EFFICAY AND SAFETY OF BCD-201 (JS BIOCAD) AND KEYTRUDA IN PATIENTS WITH UNRESECTABLE OR METASTATIC MELANOMA"

The case is an application dated 13-02-2023 from Dr. Syed Rooh Ul Arifeen Naqvi, Project Manager, DRK Pharma Solutions (Pvt) Ltd. Lahore (Contract Research Organization) wherein he has submitted Institutional Review Board (IRB) approval of **following site** with complete composition of committee i.e. names and designation of members of IRB for already approved Clinical Trial vide Registration No. CT-0051 titled as **A RANDOMIZED, DOUBLE-BLIND CLINICAL STUDY OF THE EFFICAY AND SAFETY OF BCD-201 (JS BIOCAD) AND KEYTRUDA IN PATIENTS WITH UNRESECTABLE OR METASTATIC MELANOMA**

Site(s)	**PI**	**Specialty**	**Phase of trial**
Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.	Dr. Samir Fasih, Site PI	Oncologist	Phase-III

2. It is added that Clinical Trial vide Registration No. CT-0051 is already approved for following sites.

Site(s)	PI	Specialty	Phase of trial
Shifa International Hospitals Ltd, Islamabad	Dr. Saud Ghazi (National-PI)	Oncologist	Phase- III
Shaheed Zulfiqar Ali Medical University, Islamabad.	Dr. Qasim M Buttar, Site-PI	Oncologist	Phase-III

3. The applicant submitted that M/s SKMCH&RC will also act as clinical a trial site for the subject in trial in initial application but at that time IRB approval & Notification was not attached with the initial application. Now the applicant has submitted the IRB approval of M/s SKMCH&RC, Lahore.

4. The application for approval of following new site for already registered Clinical trial is placed before Clinical Studies Committee.

Site(s)	**PI**	**Specialty**	**Phase of trial**

Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.	Dr. Samir Fasih, Site PI	Oncologist	Phase-III

Decision:

The CSC after detailed discussion and deliberation decided to approve the following additional Clinical Trial Site for already approved Clinical Trial titled, "A Randomized, Double-Blind Clinical Study of the Efficacy and Safety of BCD-201 (JS BIOCAD) and Keytruda in Patients with Unresectable or Metastatic Melanoma", under the Bio-Study Rules, 2017:

Site(s)	***PI***	***Specialty***	***Phase of trial***
Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.	*Dr. Samir Fasih, Site PI*	*Oncologist*	*Phase-III*

AGENDA ITEM VII:

Brief Title

A Study to Evaluate a PIKA-Adjuvanted Inactivated Rabies Vaccine

Official Title

A Phase III, Randomized, Comparator-Controlled, Double-Blind, Multicenter Study to evaluate the immunogenicity, safety and lot to lot consistency of three lots of a PIKA Rabies vaccine (Vero Cell) for human use, freeze dried in health adults using a post exposure prophylaxis schedule

The case is an application from Prof. Dr. Ume Sughra (CNIC 37405-0579220-0), Director research, Al-Shifa Research Centre, Al-Shifa Trust Eye hospital, Rawalpindi dated 24th February, 2023, wherein request has been made for approval of subject Clinical Trial.

US Trial Registry:

The trial is also enlisted on U.S National Trial Registry with identification number NCT05667974.

Name of investigational Product:

PIKA Rabies Vaccine (Vero Cell) for human use, freeze dried (referred to as "PIKA rabies vaccine).
Compound Name: YS-ON-001

PIKA adjuvant

PIKA adjuvant is a refined form of polyinosinic-polycyidylic acid (Poly I; C) and is a synthetic chemical analogue of a dsRNA and a Toll like Receptor 3 (TLR3) agonist is a potent immune modulator that activates the maturation of dendritic cells, proliferates B cells and NK cells, as well as promote Th1 (cellular) based immunity through its induction of IL-12 and tpe I IFNs. TLR3 is an endosomal receptor for double stranded RNA and is expressed in dendritic cells including lung cancer, breast cancer and liver cancer.

The purpose of this study is to evaluate the immunogenicity, safety and lot to lot consistency of three lots of a PIKA rabies vaccine (Vero Cell) for human use, freeze dried in Healthy Adults using a post exposure prophylaxis schedule.

Sponsor:

Yisheng Biopharma (Singapore) Pvt Ltd. (16,33,048 USD)

Brief Summary:

This is a phase III, randomized, comparator-controlled, double-blind, multi-center study to evaluate lot-to-lot consistency of three lots of a PIKA-adjuvanted inactivated rabies vaccine, immunogenicity and safety in healthy adults using a PEP schedule. It is also the aim of this study to evaluate non-inferiority and superiority of the PIKA-adjuvanted inactivated rabies vaccine compared to the rabies vaccine comparator Rabipur.

Study Description;

This is a phase III, randomized, comparator-controlled, double-blind, multi-center study to evaluate lot-to-lot consistency of three lots of a PIKA-adjuvanted inactivated rabies vaccine, immunogenicity and safety in healthy adults using a PEP schedule. It is also the aim of this study to evaluate non-inferiority and superiority of the PIKA-adjuvanted inactivated rabies vaccine compared to the rabies vaccine comparator Rabipur.

A total of 4,500 subjects will be enrolled in the study randomized into 2:1 with 3000 subjects allocated to PIKA rabies vaccine and 1,500 allocated to receive the comparator rabies vaccine Rabipur. There will be two study Groups: Group 1 (20%) and Group 2 (80%).

Within each study group, subjects will be randomly allocated in a 2:2:2:3 ratios to receive 1 of the 3 lots of PIKA rabies vaccine or Rabipur. The Rabipur group will receive the classic Essen 5 dose regimen (1-1-1-1-1 schedule on Days 0, 3, 7, 14 and 28), whilst the PIKA rabies vaccine group will receive an accelerated regimen (2-2-1 schedule with a double-dose injection on Days 0 and 3 and a single-dose injection on Day 7). For blinding purposes, normal saline will be injected on Days 14 and 28 for PIKA rabies group and Days 0 and 3 for Rabipur group.

Group 1 will enroll a total of 900 subjects, approximately 20% of the total sample population. Subjects will be randomized at 2:2:2:3 ratios (PIKA lot #1: 200 subjects, PIKA lot #2: 200 subjects, PIKA lot #3: 200 and 300 will be randomized to receive Rabipur). Blood will be collected pre-vaccination (Day 0) and post-vaccination on Days 7, 14, 28, 90, 180 and 365 to evaluate the primary immunogenicity, safety and secondary immunogenicity endpoints. Subjects will be followed up for the whole study period through clinic visits or phone calls.

The first 50 participants randomized in each of the 3 PIKA lots and that for the Rabipur will form the safety subset and will have additional blood draw for safety laboratory parameters for CBC platelet, urinalysis, serum chemistry and coagulation on Day 0 (prior to vaccination), Day 7 and Day 28.

Group 2 will enroll the remaining 3,600 subjects at 2:2:2:3 randomization ratio (PIKA lot #1: 800 subjects, PIKA lot #2: 800 subjects, PIKA lot #3: 800 and 1,200 will be randomized to receive Rabipur). Blood will be collected pre-vaccination (Day 0) and post-vaccination on Days 7 and 365 to evaluate key secondary immunogenicity endpoints of superiority, persistence and durability of immune response as well as co-primary safety objective. Subjects will be followed up for the whole study period through clinic visits or phone calls.

After each vaccination, all subjects will be observed in the clinical site for at least 30 minutes for immediate reactions and will be followed up for solicited AEs by diary cards 7 days post each vaccination and unsolicited AEs will be collected through Day 42 post first vaccination. All subjects

will be monitored for SAEs, SUSARs, AESIs, and AEs leading to study withdrawal for the whole study period.

Study Design:

Allocation: Randomized
Intervention Model: Parallel Assignment
Masking: Triple(Participant,CareProvider,Investigator)
Primary Purpose: Prevention

Intervention:

- Biological: PIKA-adjuvanted inactivated rabies vaccine

  PIKA rabies vaccine
- Biological: Rabipur

Study Arms

- Experimental: Control

  Receive 1 of the 3 lots of PIKA rabies vaccine via IM administration that 2-2-1 schedule with a double-dose injection on Day 0 and 3 and a single-dose injection on Day 7

  Intervention: Biological: PIKA-adjuvanted inactivated rabies vaccine
- Experimental: Rabipur

  Receive Rabipur via IM administration that the classic Essen 5-dose regimen 1-1-1-1-1 schedule on Days 0, 3, 7, 14 and 28

  Intervention: Biological: Rabipur

Eligibility Criteria

Inclusion Criteria:

- Has completed the written informed consent process.
- For Singapore sites: age ≥21 and ≤ 65 years on Study Day 0; for other country sites: age ≥18 and ≤ 65 years on Study Day 0.
- Healthy males and females.
- No history of rabies exposure, administration of rabies vaccination or rabies immunoglobulin.
- Agree to refrain from blood donation during the course of the study.
- Be able to commit to the vaccine schedule strictly.
- The ability and commitment to comply with requirements of the study, such as completion of diary cards, return for follow-up visits, accessible by phone and reside within the study area for the duration of study.
- For female subjects: agree to avoid pregnancy from Study Day 0 to Study Day 90 during the course of the study. Women physically capable of pregnancy (not sterilized and still menstruating or within 1 year of the last menses if menopausal) in sexual relationships with men must use an acceptable method of avoiding pregnancy during this period. Acceptable methods of avoiding pregnancy include a sterile sexual partner, sexual abstinence (not engaging in sexual intercourse), hormonal contraceptives (oral, injection, transdermal patch, or implant), vaginal ring, intrauterine device (IUD), or the combination of a condom or diaphragm with spermicide.

Exclusion Criteria:

- Pregnant and nursing female volunteers will be excluded from the study.
- Previous exposure to a suspect rabid animal within the last 12 months.
- Any subject who needs PEP against rabies.
- History of rabies infection or treatment (immunoglobulin or vaccine).
- History of previous rabies vaccination.
- History of hypersensitivity reaction to human immunoglobulin.
- Received any vaccine in the past 30 days before randomization except for Covid 19 and flu vaccination.
- Received immunoglobulin or blood products within 90 days before randomization or plans to receive such products at any time during active period of the study (through Day 90).
- Received any investigational therapy (including vaccine) within 90 days before randomization, or planned participation in any other investigational study during the active study period (through Day 90).
- Used immunosuppressant medications in the past 180 days (defined as more than 14 continuous days before randomization or plans to receive any products during the active vaccination period (through Day 28). An immunosuppressant dose of a glucocorticoid will be defined as a systemic dose of ≥10mg of prednisone per day or equivalent. The use of topical, inhaled, and nasal glucocorticoids will be permitted).
- At high risk for rabies infection during the trial: (such as veterinarians and their staff, animal handlers, rabies researchers, and certain laboratory workers, persons whose activities bring them into frequent contact with rabies virus or potentially rabid bats, raccoons, skunks, cats, dogs, or other species at risk for having rabies, people travelling where rabies is enzootic, previous bite by a rabid animal with no post-exposure treatment administered).
- History of HBV or HCV infection.
- History of any past, present, or future possible immunodeficiency state including but not limited to any laboratory indication of HIV-1 infection.
- History of treatment for depression or mental illness in the past 5 years; history of any attempt of suicide.
- Bleeding disorder, or receipt of anticoagulants in the past 21 days preceding inclusion, contraindicating IM vaccination based on Investigator's judgment.
- Donation of blood within the last 2 months or who have donated plasma within the last 14 days before Study Day 0.
- Clinical signs of encephalitis.
- History or evidence on physical examination of any systemic disease or any acute or chronic illness that, in the opinion of the investigator, may interfere with the evaluation of the safety or immunogenicity of the vaccine.
- History of neurological disorder, either congenital or acquired (e.g. seizures, meningitis, encephalitis, Guillain-Barre syndrome, dementia, vasculitis, hereditary CNS disorders).
- History of cancer (malignancy) in the past 10 years (exception is non-melanomatous skin CA).
- A history of alcohol or drug addiction in the past 2 years.
- History of hypersensitivity or serious reactions (e.g. anaphylaxis, urticarial, other significant reaction) to previous vaccinations.
- Plans to permanently move from the catchment area during trial conduct.
- Concerns of compliance with protocol or social condition that makes the subject a poor candidate for the trial as determined by the PI.

The details of the submitted documents are as under;

Sr.	Documents	Remarks	
1	Application on prescribed Form-II	Attached	
2	Prescribed Fee	Rs. 200,000/- deposited vide slip number 011828005120	
3	Investigator Brochure (s)	Version 6.0, Dated: 4th August, 2022 is attached.	
4	Final protocol	Attached YS-002 Version 2.2 dated 27-01-2023	
5	Informed consent and participant information sheet (Urdu to English)	Attached.	
6	List of participating countries	Singapore Pakistan Philippines	
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.	PIKA rabies Vaccine: 1500 Comparator (Rabipur): 800 Total: 2300	
9	Site of the trial	SITE	PI
		Al-Shifa Research Center, Al Shifa Trust Eyes Hospital Rawalpindi	Prof Dr. Ume Sughra, Epidemiologist
		Ziauddin University and Hospital Clifton Karachi	Dr. M. Osama Rehman Khalid, Consultant Physician
		Central Park Teaching Hospital, Lahore	Dr. M. Ahmad, Pulmonologist
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Al-Shifa Research Center, Al Shifa Trust Eyes Hospital Rawalpindi	21-Feb 2023
		Ziauddin University and Hospital Clifton Karachi	28.02.2023
		Central Park Teaching Hospital, Lahore	IRB-02002-116
11	Approval of National Bio-ethics Committee (NBC)	NBC approval reference letter No.4-87/NBC-937/23 dated 24-02-2023	
12	CV's of the Investigators	CVs of following (PI) expert is attached.	

		i. Prof Dr. Ume Sughra, Epidemiologist ii. Dr. M. Osama Rehman Khalid, Consultant Physician iii. Dr. M. Ahmad, Pulmonologist
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP and COA certificate attached. Liaoning Yisheng Biopharma Co., Ltd.
14	Pre-clinical/clinical safety studies	Phase-I NCT02657161 (completed) Phase-II NCT 02956421 (completed) Phase-III approved in Singapore vide approval number CTA2200082 dated 20-07-2022.
15	Summary of Protocol	Attached in Protocol.
16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	1500 in Pakistan (Competitive Recruitment)
19	Name of Monitors & Clinical Research Associate	Dr. Syed Rooh Ul Arifeen Naqvi Mobeen Amjad Hafiz Anwar Ul Huda Nasir Abbas Shiza Ashraf Fahad Ali Awan Alishba Mushtaq Abida Hashmi Tooba Tahir
20	Evidence of registration in country of origin.	N/A
21	Copy of registration letter (if registered in Pakistan)	N/A
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	18 Months
23	Undertaking on Stamp paper	Attached.

IMPs required along with justification:

Intervention name	PIKA rabies Vaccine	Rabipur
Sourcing	Liaoning Yisheng Biopharma Co., Ltd.	GSK Singapore
Main ingredients	PIKA Rabies vaccine	Rabies Vaccine
Formulation	1 ml	1 ml
Dose regimen and route of administration	1 ml	1 ml
Storage	2 C to 8 C	2 C to 8 C

Decision:

The CSC after detailed discussion and deliberation decided to approve:

1. *Clinical Trial titled, "A Phase III, Randomized, Comparator-Controlled, Double-Blind, Multicenter Study to evaluate the immunogenicity, safety and lot to lot consistency of three lots of a PIKA Rabies vaccine (Vero Cell) for human use, freeze dried in health adults using a post exposure prophylaxis schedule", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site(s):*
    - *Al-Shifa Research Center, Al Shifa Trust Eyes Hospital Rawalpindi*
    - *Ziauddin University and Hospital Clifton Karachi*
    - *Central Park Teaching Hospital, Lahore*
2. *Quantities of IMP will be imported after getting necessary approval/NOC from concerned DRAP field office*

PIKA rabies Vaccine: 1500
Comparator (Rabipur): 800
Total: 2300

AGENDA ITEM VIII:

APPLICATION FOR LICENSE TO ACT AS CLINICAL TRIAL SITE FROM M/S AKRAM MEDICAL COMPLEX, LAHORE. (F.No.15-23/2023 DD (PS)).

The case is an application from Dr. Shehla Javed Akram, CNIC CNIC:35202-9317913-0 of M/s Akram Medical Complex, 2B Ayesha Siddiqa Road, Main Gulberg, Lahore, wherein she has applied to act as Clinical Trial Site for phase I, II, III & IV clinical trials. The application is on Form-I of the Bio-Study Rules 2017 without prescribed fee of Rs. 100,000/-.

2. It is submitted that application evaluated according pre- requisites as mentioned in Form-I of the Bio-Study Rules 2017, and as following are observations:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	**Not Attached.**
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	**Not Attached.**
4	Details of premises including layout plan of the site.	Layout plan of Akram medical complex Attached. **Layout plan of CTS along with details required.**
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Attached. **List of equipment required for Bio-analytical Lab is required.**
6	Names and qualifications of the above sections along with their staff.	List Attached. **CVs of staff working at CTS required.**

7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Attached.
8	Undertaking on stamp paper	**Not Attached.**

3. In the light of above, following shortcoming has been observed.

i. Prescribed processing fee not attached.
ii. Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors (registered from registrar for firm or SECP) required.
iii. Layout plan of CTS along with details required.
iv. List of equipment required for Bio-analytical Lab is required
v. CVs of staff working at CTS required.
vi. Undertaking on stamp paper.

4. The shortcomings have been communicated to applicant and reply is still awaited.

Decision: -

The CSC decided and delegated its power to the Chairman CSC for constitution of the panel for inspection. Meanwhile, applicant advised to fulfill following shortcomings:

i. Prescribed processing fee not attached.
ii. Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors (registered from registrar for firm or SECP) required.
iii. Layout plan of CTS along with details required.
iv. List of equipment required for Bio-analytical Lab is required
v. CVs of staff working at CTS required.
vi. Undertaking on stamp paper.

4. The case was placed before CSC in its 38th meeting held on 08.02.2023 and was decided as follows;

The CSC decided and delegated its power to the Chairman CSC for constitution of the panel for inspection. Meanwhile, applicant advised to fulfill following shortcomings:

i. Prescribed processing fee not attached.
ii. Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors (registered from registrar for firm or SECP) required.
iii. Layout plan of CTS along with details required.
iv. List of equipment required for Bio-analytical Lab is required
v. CVs of staff working at CTS required.
vi. Undertaking on stamp paper.

In response to this office letter F.No. 16-38/2023 dated 13th February 2023, the applicant has submitted reply. The reply has been evaluated in tabulated Form as following;

Shortcoming	Reply

Prescribed processing fee not attached.	Original Fee Slip No 96124113400 dated 22.12.2023 attached.
Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors (registered from registrar for firm or SECP) required.	The property Transfer documents attached.
Layout plan of CTS along with details required.	Attached.
List of equipment required for Bio-analytical Lab is required	Attached but don't have equipment required for Bio-Analytical Lab.
CVs of staff working at CTS required.	Attached.
Undertaking on stamp paper.	Attached.

6. Accordingly following panel was constituted vide this office letter dated 22.02.2023;
   d. Prof. Dr. Nadeem Irfan Bukhari, College of Pharmacy, University of the Punjab, Lahore.
   e. Dr. Farhana Badar, Bio-Statistician, SKCH&RC, Lahore.
   f. Mr. Ahsan-Ul-Haq Athar, Deputy Director, DRAP, Islamabad **(Coordinator).**

   The panel conducted the inspection on 24.02.2023 as per checklist and recommended the site for approval with following remarks.
   "Keeping in view the staff qualification, research experience, facilities at site, laboratory, electricity backup, research publications, IT facility and attitude toward improvement, the panel recommended the site for approval for phase III & IV. Also recommended for phase II for already registered therapeutic goods with Stringent Regulatory Authorities (SRAs) for trials on new indications."

   Recommended for approval ***(for phase III & IV. For phase II only for registered therapeutic goods with RRAs for trials with new indications).***

Decision:

The CSC in pursuance to the recommendations of the inspection panel & in the light of discussion/deliberations unanimously decided to renew the licence of M/s M/s Akram Medical Complex, 2B Ayesha Siddiqa Road, Main Gulberg, Lahore to act as Clinical Trial Site for Phase- III & IV Generalized Clinical Trials and Phase II only for registered therapeutic goods with RRAs for new indications only, under the Bio-Study Rules, 2017.

AGENDA ITEM IX:

APPLICATION FOR APPROVAL OF APPLICATION TO ACT AS CRO AT M/S ASA RESEARCH VENTURE PVT. LIMITED, LAHORE (15-19/2022 DD (PS)).

The case is an application from Dr. Shehla Javed Akram, CNIC:35202-9317913-0, Managing Director, M/s ASA Research Venture (Pvt.) Ltd, 49-Mozang, Road Lahore, wherein the request has been made for license act as Clinical Research Organization (CRO). The application is on prescribed Form-I of the Bio-Study Rules 2017 along with a fee of Rs.300000/- submitted vide Slip number 3759275006, dated 12th August 2022.

2. It is submitted that application evaluated according pre-requisites as mentioned in Form-I of the Bio-Study Rules 2017, summary of submitted documents is as follows:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed fee challan	Attached
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	SECP Certificate Incorporation, Articles of association are attached.
4	Details of premises including layout plan of the site.	Layout attached.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Not applicable as applied for CRO.
6	Names and qualifications of the above sections along with their staff.	The staff name and CVs attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Not applicable as applied for CRO.
8	Undertaking on affidavit	Attached

3. In the light of above, it is proposed that as per practice, the inspection of the premises may be conducted to check the suitability of the proposed Contract Research organization.

The case was placed before CSC in its 38th meeting held on 08.02.2023 and was decided as follows;

The CSC decided and delegated its power to the Chairman CSC for constitution of the panel for inspection. The panel report will be placed before CSC for its consideration.

The following panel was constituted vide this office letter F.No. 15-19/2022 dated 21.02.2023, the following panel was constituted;

i. Prof. Dr Nadeem Irfan Bukhari, College of Pharmacy, University of the Punjab, Lahore.
ii. Dr. Farhana Badar, SKMCH&RC, Lahore.
iii. Ahsan Ul Haq Athar, Deputy Director, DRAP, Islamabad (**Coordinator**).

The panel conducted the inspection on 24.02.2023 and has submitted the inspection report as per check list and recommended the proposed CRO for approval with following remarks;

"*Keeping in view the staff training, experience, qualification, IT facility, storage area, energy backup, firefighting system, the panel recommended for approval to act as CRO. The management was advised to improve archiving room and electronic data security and they agreed."*

- ***Recommended for approval***

Submitted for consideration of CSC.

Decision:

The CSC in pursuance to the recommendations of the inspection panel & in the light of discussion/deliberations unanimously decided to grant the licence to M/s ASA Research Venture (Pvt.) Ltd, 49-Mozang, Road Lahore to act as Contract Research Organization, under the Bio-Study Rules, 2017.

AGENDA ITEM X:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL SITE SITUATED AT PAKISTAN INSTITUTE OF OPHTHAMOLOGY, AL SHIFA TRUST EYE HOSPITAL RAWALPINDI FOR PHASE I, II, & IV. F. No.15-17/2022 DD (PS)

Application was received from Brig. (R) Rizwan Ullah Asghar (Executive Director) NIC number 31202-0257073-I of M/s Al- Shifa Trust Eye Hospital, Jehlum Road Rawalpindi, wherein he has requested for grant of licence to act as clinical trial site for phase I, II, III. The application is on Form-I of the Bio-Study Rules 2017 along with prescribed fee of Rs. 100,000/- submitted vide slip number 747255245 dated 19.09.2022.

2. It is submitted that application evaluated according pre- requisites as mentioned in Form-I of the Bio-Study Rules 2017, and as following are observations:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	Fee challan of Rs.100,000/- submitted vide slip number 747255245 dated 19.09.2022.
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	Certificate of Registration by Islamabad Capital Territory administration, Certificate of Registration of Societies, Memorandum & Articles of Association, Letter of Authority, Memorandum of Association, Rules & Regulations, List of Board of Governors, Board of Trustees and Registration certificates by Punjab Healthcare Commission are attached.
4	Details of premises including layout plan of the site.	Layout plan of proposed CTS attached.
5	Details of the section wise equipment and machinery	List of equipment attached.

	required for the analytical or bio-analytical and clinical studies.	
6	Names and qualifications of the above sections along with their staff.	Section wise details regarding personal/ experts not provided whereas CVs of followings are attached. 1. Mr. Asif Iqbal, QCM, 2. Miss Amara Sani, Microbiologist, 3. Miss Khadija Bibi, Sr. QC Analyst, 4. Miss Samara Rashid, QC Analyst. 5. Prof. Dr. Ume Sughra, 6. Dr. Mariam Suleman, 7. Dr. Asma Riaz, 8. Dr. Rasikh Arif etc.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	SOP for Emergency Medical Services is attached.
8	Undertaking on stamp paper	Attached.

3. The Chairman CSC nominated following panel for inspection & decision communicated vide letter bearing even number dated 20th December, 2022.

i. Brig. (R) Dr. Muzammil Hasan Najmi
ii. Malik Muhammad Asad
iii. Hafiz Muhammad Jawad
iv. Shafqat Hussain Danish.

4. Accordingly, panel inspected the subject site on 27th February, 2023 & submitted inspection report with following remarks:

The panel of experts nominated vide letter No. F.No.15-17/2022, dated 24-02-2023, inspects the CTU on 27.02.2023 for verifying the facility to conduct CT Phase-I, II, III & IV. It was observed that, no facility for Pk/Pd, bioanalytical assay was present. Therefore, it was informed that the CTU will perform only Clinical & Pathological part of Phase I & II Clinical trial/study, whereas, Pk/Pd portion will be the responsibility of the Sponsor.
The panel suggested some improvements w.r.t. emergency evacuation plan, SOPs for material transfer (quarantine area), GSP adherence, IPC practices and cleaning & disinfection of facility, but as a whole the required human resources, equipment, and services were upto the mark. The team was very professional and top management shows commitment for continual improvements.
The panel unanimously approved the CTU for Phase-I, II, II & IV Clinical trials, except for Pk/Pd parts (being responsibility of the Sponsor)

Concluding status of inspection / application

- **Recommended for approval**

Decision:

The CSC in pursuance to the recommendations of the inspection panel & in the light of discussion/deliberations unanimously decided to approve the site of M/s Al-Shifa Research Center at Shifa Trust Eye Hospital Rawalpindi for Phase-I, II and IV Clinical Trials except their PK/PD parts, which would be the responsibility of Sponsor, under the Bio-Study Rules, 2017.

Further, it was decided that, approval to act as Clinical Trial Site for Phase-I, II & IV will be incorporated in previously issued licence (CTS-0044) for Phase-III with same validity as already approved.

AGENDA ITEM XI:

APPLICATION FOR REGISTRATION AND APPROVAL OF CLINICAL TRIAL "A RANDOMIZED, DOULE BLIND, PLACEBO CONTROLLED TO EVALUATE THE PERFORMANCE AND SAFETY OF SPL 7013 SPRAY IN NON-HOSPITALIZED PATIENTS WITH COVID-19" (F.No.03-23/2023 DD (PS).

The case is an application from Dr. Sohail Anwar, CNIC No.35202-2604099-5, M/s University College of Medicine and Dentistry, The University of Lahore, 1Km Defence Road, Bhupatian Chowk, Off Raiwind Road, Lahore, wherein request has been made for approval of subject Clinical Trial. Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide Slip number. 1358724724, dated 9th January, 2023.

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

v. **Sponsor:** Starpharma Pty Limited, 4-6 South Ampton Crescent Abbotsford, Victoria 3067, Australia.

Brief Summary: SPL7013 Nasal Spray is intended to trap and block cold and respiratory viruses in the nasal cavity before an infection develops fully. SARS-CoV-2 (coronavirus) is a respiratory virus that can lead to the respiratory illness, COVID-19. Symptoms of COVID-19 include, but are not limited to, fever (high body temperature), coughing, sore throat, fatigue (tiredness), and shortness of breath, and the disease has been associated with hospital intensive care admissions and a significant death rate. Viruses, like SARS-CoV-2, act by attaching themselves to receptors on human cells. Attachment to these receptors allows the virus to enter, or infect, these cells and cause replication of the virus that is then released from the cells and can infect other cells in the body. The receptors that SARS-CoV-2 binds to are found in high numbers on cells that line the nasal cavity, and these cells are a key target for initial infection. Therefore, it has been proposed that a product that can stop respiratory viruses such as SARS-CoV-2 from accessing and attaching to the cells in the nasal cavity could help prevent or treat respiratory disease by reducing exposure to viruses.
SPL7013 Nasal Spray works by forming a barrier that contains a molecule called SPL7013, which can trap viruses before they access and attach to cells. The nasal spray containing SPL7013 is a medical device registered and marketed in several European countries and in the UK under the brand name, Viraleze™.
SPL7013 Nasal Spray has been applied to the nasal cavity of healthy volunteers under controlled conditions in a clinical trial and was demonstrated to be well tolerated when used four times a day for 14 days. The aim of this study is to add to the current data by testing the performance and safety of SPL7013 Nasal Spray in COVID-19 patients. The aim is to determine the performance of SPL7013 Nasal Spray at reducing the amount of SARS-CoV-2 virus in the nasal cavity of people with COVID-19, and to assess if there are any adverse effects.

Who can participate?
Adults over the age of 16 years with a recent diagnosis of COVID-19. This investigation is not open to women who are pregnant, planning to become pregnant or breastfeeding.

What does the study involve?
Participants with a positive PCR test for COVID-19 will be randomly allocated to the SPL7013 Nasal Spray group or the control group. Participants in the control group will receive the placebo nasal spray, which is a spray that does not contain SPL7013. Participants will use the nasal spray four times daily for 7 days. During these 7 days, participants will take swabs daily to allow for measuring the amount of virus in the nasal cavity, and complete an online questionnaire about symptoms and other medical information. Participants will attend a final visit to the site on Day 8 to return their nasal spray and

undergo a final examination by the investigator.

What are the possible benefits and risks of participating?
For those allocated to SPL7013 Nasal Spray, use of the spray may reduce the amount of virus in the nasal cavity, which may help to ease or reduce symptoms and help with recovery. No benefits are anticipated for those randomised to placebo nasal spray.
In a previous study of SPL7013 Nasal Spray in healthy volunteers, a small number of participants reported headache, nasal discomfort, nasal congestion, runny nose or nosebleed. These events were observed at similar rates in both SPL7013 Nasal Spray and placebo-treated participants. There may be additional adverse effects in humans that are not yet known. As with any other treatment, there is the potential risk of anaphylaxis - a severe allergic reaction that can cause itchy rash, throat swelling, and a drop in blood pressure, although this type of reaction has not previously been observed with products containing SPL7013.

ii. Study IMPs required along with justification:

Intervention name	**SPL7013**	**Placebo**
Sourcing	Starpharma Pty Limited, 4-6 South Ampton Crescent Abbotsford, Victoria 3067, Australia.	Starpharma Pty Limited, 4-6 South Ampton Crescent Abbotsford, Victoria 3067, Australia.
Specification	1% W/W	Normal Saline
Main ingredients	Astodrimer Sodium	Normal Saline
Formulation	Nasal Spray	Nasal Spray
Appearance	Non sterile aqueous based solution	Non sterile aqueous based solution
Dose regimen and route of administration	One spray actuation 4 time a day in each Nostril. One actuation delivers volume of 100µl. Approximate daily delivered volume 900µl.	One spray actuation 4 time a day in each Nostril. One actuation delivers volume of 100µl. Approximate daily delivered volume 900µl.

iii. Quantity of IMD required along with justification:

Study Intervention	**Test Drug**	**Placebo**
Intervention Name	SPL7013	Placebo
Dose Formulation	Nasal Spray	Nasal Spray
Each Bottle Contains	10ml/ Bottle	10ml/ Bottle
Quantity to be imported	200 Kits or 320 + 80 bottles	
Total box to be imported	200 Carton (2 Bottles/ Carton)	
Total subjects to be recruited in Pakistan	80	

iv. Number of subjects to be recruited: **160 Subjects** (Globally)

v. Anticipated cost of the project: Rs 27551.53/Subject-

vi. Study design & details:

Study Type	Interventional (Clinical Trial)
Estimated Enrollment :	**160** participants (Globally)
Allocation:	Randomized
Intervention Model:	Parallel Assignments
Masking:	Research Team, Participant, investigator and staff

Official Title:	A RANDOMIZED, DOULE BLIND, PLACEBO CONTROLLED TO EVALUATE THE PERFORMANCE AND SAFETY OF SPL 7013 SPRAY IN NON-HOSPITALIZED PATIENTS WITH COVID-19

The study will be carried out at mentioned sites comprising of following primary objective(s);

Site(s)	PI	Specialty	Phase of trial	Remarks
University College of Medicine and Dentistry, The University of Lahore.	Dr. Sohail Anwar	Pulmonologist	**Post Market Confirmatory.**	**Phase of trial not mentioned.**

Primary & Secondary Objectives

i. To evaluate the performance of SPL7013 Nasal Spray compared with placebo in reducing SARs-CoV-2 viral burden in the nasopharynx.
(Primary)

ii. To evaluate the performance of SPL 7013 Nasal Spray compared with placebo in preventing the progression of mild to moderate cases of Covid-19.

iii. To evaluate the safety and tolerability of SPL7013 Nasal spray when applied to the Nasopharyngeal mucosa of patients with mild to moderate Covid-19.

3. The details of the submitted documents are as under;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs. 200,000/- deposited vide Slip number. 1358724724, dated 9th January, 2023
3	Investigator Brochure (s)	English Language
4	Final protocol	Attached
5	Informed consent and participant information sheet (Urdu to English)	Attached.
6	List of participating countries	Pakistan, UK
7	Phase of trial.	**Post Market Confirmatory Clinical Investigation.**
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.	SPL7013 + Placebo = 200 IMD Kits or 400 bottles of nasal Spray. **Quantities to be imported are not justified.**
9	Sites of the trial	University College of Medicine and Dentistry, The University of Lahore.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached.
11	Approval of National Bio-ethics Committee (NBC)	Approved vide Ref: No.4-87/Covid-123/22/929 dated 5th January 2023.
12	CV's of the Investigators	CVs of following Dr. Sohail Anwar is attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP certificate of **Conforma NV,** Zenderstraat 10, Destelbergen, 9070, Belgium attached.

14	Pre-clinical/clinical safety studies.	**Not Attached.**
15	Summary of Protocol	Given in protocol.
16	Summary of Investigator Brochure	Given in Investigator Brochure.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	80 in Pakistan
19	Name of Monitors & Clinical Research Associate	**Miss** Sadaf , Farooq Ahmed, Haziqa Tehreem.
20	Evidence of registration in country of origin.	**Product not registered yet.**
21	Copy of registration letter (if registered in Pakistan)	**Not applicable.**
22	Sample of label of the investigational product / drug.	**Sample label given for 250mg powder with direction of IM Use and manufacturer is XXX Pharmaceutical Switzerland.**
22	Duration of trial	8 months
23	Undertaking on Stamp paper	Attached.

After administrative scrutiny of documents submitted, following observations/ shortcomings has been noticed.

i. Phase of trial mentioned in application is Post Market Confirmatory Clinical Investigation, the data of phase I, II & III clinical/ Pre-clinical/ Clinical safety studies is required.
ii. Quantities to be imported are not justifies.
iii. CoPP/ Free Sale Certificate is required.
iv. Sample label given for 250mg powder with direction of IM use and manufacturer is XXX Pharmaceutical Switzerland.
v. Clarification regarding IMD manufacturer and its GMP certificate with section to manufacture Medical devices is required.
vi. Justification regarding too small size of subjects for post market surveillance.
vii. Insurance details of the subjects is required.

Decision: -

The CSC gave an opportunity to Mst. Ghazala Rubi, on behalf of sponsor, to present the case and address the shortcomings but due to IT issues or some other reasons her voice was not audible. The CSC deferred the case with direction to applicant to submit the reply to the following queries/ shortcomings;

i. Phase of trial mentioned in application is Post Market Confirmatory Clinical Investigation, the data of phase I, II & III clinical/ Pre-clinical/ Clinical safety studies is required.
ii. Quantities to be imported are not justifies.
iii. CoPP/ Free Sale Certificate is required.
iv. Sample label given for 250mg powder with direction of IM use and manufacturer is XXX Pharmaceutical Switzerland.
v. Clarification regarding IMD manufacturer and its GMP certificate with section to manufacture Medical devices is required.
vi. Justification regarding too small size of subjects for post market surveillance.
vii. Insurance details of the subjects is required.

Sr. #	*Observations*	*Firm's Response*
	Phase of trial mentioned in application is Post Market Confirmatory Clinical Investigation, the data of phase I, II & III clinical/ Pre-clinical/ Clinical safety studies is required.	*The requested clinical data is not applicable for medical devices, because SPL7013 nasal spray is not a drug but a class- I medical device. As per EU Directives Class-I medical devices required biological evaluations as per ISO-10993. [It conforms the biocompatible and cytotoxic behavior of the device].* *Further clarification for this query: -* *i. Chemical, Physical and biological properties;* *ii. Infection and microbial contamination;* *iii. Construction and environmental properties;* *iv. Non clinical data already submitted.* *v. Clinical studies summary already submitted*
	Quantities to be imported are not justifies.	*A total 200 blinded investigational medical device kits containing two bottles each(i.e., 400 spray bottles) will be imported in Pakistan as of +25 overage.*
	CoPP/ Free Sale Certificate is required.	Copy of Free Sale Certificate of Netherland of above mentioned product "Viraleze Nasal Spray".
	Sample label given for 250mg powder with direction of IM use and manufacturer is XXX Pharmaceutical Switzerland.	Label text provided.
	Clarification regarding IMD manufacturer and its GMP certificate with section to manufacture Medical devices is required.	Certificate of GMP compliance of manufacturer of Conforma, NV Belgium, is attached.
	Justification regarding too small size of subjects for post market surveillance.	*The sample size has been selected to fulfil the primary the primary objective of the investigation with a 90% power.*
	Insurance details of the subjects is required.	*The insurance for the clinical trial participants has been bound with CHUBB Insurance Australia, ltd., Melbourne Australia.* *[CHUBB IS A REGISTERED COMPANY IN Pakistan with company registration number, 0042752 dt. 06-08-2001 with NTN number 2295312-4.*

Discussion:

The case placed before the Committee, Mr. Alex from UK, representative of Sponsor joined the meeting & replied the queries raised by CSC members. He appraised the Committee that, the product under investigation is not a drug but Class-I (Low Risk) Medical Device. He further explained that, the Sponsor has performed Non-Clinical Bio-Compatible Studies & a Clinical Investigation that is equivalent of Phase-I Clinical Safety Study in order to satisfy the requirements of Medical Device regulations. He said trial is about a medical device (IMD) and is not treated as a drug. Hence, it does not require phase I, II, II clinical trials. Further, the product is registered in Netherlands and has CoPP from concerned Authority. He further explained that, SPL7013 nasal spray provides non-antimicrobial nasal dressing that moisturizes & physically traps & blocks extracellular respiratory/cold viruses in nasal cavity, thus reducing viral load. This nasal spray is therefore classified as a medical device, based on the intended use of the product & its principle mode of action, which is achieved by physical means & not by pharmacological, immunological or metabolic means. He also appraised that medical devices are required to undergo biological evaluation as per ISO10993. SPL7013 Nasal Spray has undergone bio-compatibility testing for Cyto-toxicity (ISO-10993-5), nasal irritation, following repeated administrations in the rat (ISO-10993-10) and skin sensitization in guinea pig (ISO-10993-10). Results of these bio-compatibility studies demonstrated that SPL7013 nasal spray is non-toxic, non-irritant & non-sensitizer. Clinical investigation SPL7013-021 showed that, SPL7013 nasal spray was safe well tolerated & not absorbed into blood stream following application in humans. The clinical development stage is post market confirmatory clinical investigation as per ISO-14155:2020.

Decision:

The CSC after detailed discussion and deliberation decided to approve the;

i. *Clinical Trial titled, "A RANDOMIZED, DOULE BLIND, PLACEBO CONTROLLED TO EVALUATE THE PERFORMANCE AND SAFETY OF SPL 7013 SPRAY IN NON-HOSPITALIZED PATIENTS WITH COVID-19" to be conducted at University College of Medicine and Dentistry, The University of Lahore.*
ii. *Quantities to be imported SPL7013 + Placebo = 200 IMD Kits or 400 bottles of nasal Spray.*

AGENDA ITEM XII:

ANTICOAGULATION FOR STROKE PREVENTION IN PATIENTS WITH RECENT EPISODES OF PERIOPEARATIVE ATRIAL FIBRILLATION AFTER NONCARDIAC SURGERY- THE ASPIRE-AF TRIAL (F.No.03-34/2023 DD (CTS-1)).

The case is an application from Dr. Saeed Ullah Shah (CNIC 17301-4566737-3), Consultant Cardiologist, Shifa International Hospitals Ltd, H-8/4, Islamabad dated 20th February, 2023, wherein request has been made for approval of subject Clinical Trial.

2. Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide slip number 799831064.

3. The trial is also enlisted on U.S National Trial Registry with identification number NCT03968393.

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

i. **Sponsor: Population Health Research Institute Canada**

5. **Brief Summary:**

This is a Phase-IV prospective, randomized, open label clinical trial with blinded outcome assessment (Probe Design). Patients will be randomized to a non-vitamin K oral anticoagulants NOACs (intervention arm) or no anticoagulation (control arm).

6. The details of the submitted documents are as under;

Sr.	Documents	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs. 200,000/- deposited vide slip number 799831064
3	Investigator Brochure (s)	Version 2.0, Dated: 4th August, 2022 is attached.
4	Final protocol	Attached ASPRE-AF Protocol v4.0 dated 29-10-2021
5	Informed consent and participant information sheet (Urdu to English)	Attached.
6	List of participating countries	Argentina Australia Brazil Canada Denmark India Italy Nepal Netherlands New Zealand Sweden Pakistan Spain UK
7	Phase of trial.	Phase – IV
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.	**Test Drug:** Xarelto 20mg tablet To be purchased from Shifa Pharmacy
9	Site of the trial	**Site(s)** **PI** **Shifa International Hospitals Ltd, Islamabad** Dr. Saeed Ullah Shah
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached. IRB# 0135-22
11	Approval of National Bio-ethics Committee (NBC)	NBC approval reference letter No.4-87/NBC-813/22/110
12	CV's of the Investigators	CVs of following (PI) expert is attached. iv. Dr. Saeed Ullah Shah, Consultant Cardiologist, Shifa International Hospitals Ltd Islamabad.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP certificate attached. CoPP attached.
14	Pre-clinical/clinical safety studies	Already marketed drug; so no pre-clinical, clinical and safety studies data is required.
15	Summary of Protocol	Attached in Protocol.

16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	36 Subjects in Pakistan (Competitive Recruitment)
19	Name of Monitors & Clinical Research Associate	Dr. Tehreem Zahid. CRA Dr. Sundus Dadan. CRA Dr. Palwasha Alavi. CRA Raja Waseem Akram. Research Pharmacist
20	Evidence of registration in country of origin.	Product is registered in Pakistan
21	Copy of registration letter (if registered in Pakistan)	Attached.
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	The duration of participation of each individual subject is **24 months** from the consent to last visit.
23	Undertaking on Stamp paper	Attached.

(1) Title of trial or study: ANTICOAGULATION FOR STROKE PREVENTION IN PATIENTS WITH RECENT EPISODES OF PERIOPEARATIVE ATRIAL FIBRILLATION AFTER NONCARDIAC SURGERY- THE ASPIRE-AF TRIAL.

(2) Control number: F.No.03-34/2023-CTS-1 (PS)

(3) Approved protocol version: ASPRE-AF Protocol v4.0 dated 29-10-2021

(4) Phase of trial or type of study: Phase – IV

(5) Purpose/Objective of trial or study: The purpose of this study is to determine the efficacy and safety of non-vitamin K oral anticoagulation (NOACs) versus no anticoagulation in patients with perioperative AF.

(6) Investigational products;

S.No.	Chemical name:	Non-proprietary name:	Trade name (if any):	Manufacturer:
01	N/A	Rivaroxaban tablets	Xarelto	M/s Bayer Pakistan (Private) Limited Karachi

(7) Applicant details;

(a) **Name:** Dr. Saeed Ullah Shah

(b) **Designation:** Consultant Cardiologist, Shifa International Hospitals Ltd Islamabad.

(8) Principal investigator(s):

S.No.	Name	CNIC No.	Position	Institute	Trial Site
01	Dr. Saeed Ullah Shah	CNIC 17301-4566737-3	Principal Investigator	Shifa International Hospital, Islamabad.	Shifa Research Clinical Center, Shifa International Hospital, Islamabad. (CTS-0026)

(a) **Name:** Dr. Saeed Ullah Shah (**e) CNIC No.** CNIC 17301-4566737-3

(b) **Position:** Consultant Cardiologist. (c) **Institute:** Shifa International Hospital, Islamabad. (d) **Site(s):** i. Shifa Research Clinical Center, Shifa International Hospital, Islamabad. (CTS-0026)	
(9) No. of patients to be enrolled: 36 Subjects in Pakistan (Competitive Recruitment)	
(10) Maximum duration of trial or study: 24 Months	
(11) Further conditions, if any: Nil	
(12) Quantity of IMPs need to be imported: 20mg of one tablet for one patient/day (total patients=36) so 26,280 tablets of 20mg Xarelto will be purchased from local Shifa Pharmacy.	
(13) Sponsor: Population Health Research Institute Canada	
(14) Anticipated cost of the project: 460 CAD/Patient	

ii. IMPs required along with justification:

Intervention name	**Xarelto (Rivaroxaban tablets)**	**No Anticoagulation**
Sourcing	M/s Bayer Pakistan (private) Limited, Karachi Manufactured by M/s Bayer Pharma Germany)	N/A
Specification	20 mg Tablet	N/A
Main ingredients	Rivaroxaban	N/A
Formulation	Tablet	N/A
Dose regimen and route of administration	20 mg daily Oral	N/A
Storage	15 C to 30 C	N/A
Batch number and expiration date	To be determined	To be determined

iii. Source of Investigational Medical Products (IMPs):

Pakistan

iv. Study design & details:

Study Design	Interventional (Clinical Trial Phase IV)
Estimated Enrollment :	2800 participants (Globally)…. 36 patients in Pakistan
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Open Label
Primary Purpose:	Prevention

7. The study will be carried out at mentioned sites comprising of following primary objective(s);

Site(s)	**PI**	**Specialty**	**Phase of trial**	**Remarks**
Shifa International Hospitals Ltd, Islamabad	Dr. Saeed Ullah Shah (National-PI)	Consultant Cardiologist	Phase-IV	---

Primary Objectives:

i. To assess the effects of non-vitamin K oral anticoagulants (NOACs) versus no anticoagulation on the co-primary composite outcomes of….1……non-hemorrhagic stroke and systematic embolism….2…. vascular mortality and non-fatal, non-hemorrhagic stroke, myocardial infarction, peripheral arterial thrombosis, amputation and symptomatic venous thromboembolism 24 months after randomization.

Secondary Objectives:

ii. To assess the effects of NOACs on the incidence of the following outcomes 24 months after randomization….1…. individual components of the co-primary outcomes…. 2……all cause stroke….3…. all-cause mortality.

Decision:

The CSC after detailed discussion decided to defer the Clinical Trial titled, "Anticoagulation for Stroke Prevention in Patients with Recent Episodes of Perioperative Atrial Fibrillation After Non-Cardiac Surgery- The Aspire-AF Trial" for further deliberations on following specific queries:

i. Details regarding antidote of Rivaroxaban in case of any untoward event/toxicity.
ii. Purpose of the study is not elaborating advantages of the study regarding safety/efficacy.
iii. Why control group has not been given any sort of intervention for comparison (as per the study protocol submitted).
iv. What are the advantages of the study over other anticoagulants available in the market. (e.g. Warfarin, Heparin etc.)

AGENDA ITEM XIII:

APPLICATION FOR APPROVAL OF A PHASE-III CLINICAL TRIAL TITLED "COVID-19 mRNA VACCINE (RBMRNA-405) AS A BOOSTER DOSE IN ADULTS WHO COMPLETED 2 DOSES OF INACTIVATED VACCINATION", FROM CBSCR-ICCBS, KARACHI. F. No.03-14/2022-CT(PS).

Application was received from Dr. Raza Shah CNIC: 42201-4178970-1), General Manager, CBSCR, Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, University Road, Karachi, dated 10th November, 2022, received on 16th November, 2022. 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. 083606668, dated 11th November, 2022.

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

i. **Sponsor:** M/s Argorna Pharmaceuticals Co., Ltd, China.
ii. Purpose of trial: The clinical trial is designed to be randomized, blind, parallel positive controlled, phase III clinical trial to evaluate immunogenicity and safety of RBMRNA-405 as a booster dose in subjects aged 18 years old and above who have completed immunization with two doses of inactivated vaccine.
iii. Arms & Interventions:

Investigational Product	Control Product
• Product name: COVID-19 mRNA vaccine (RBMRNA-405) • Manufacturer: Guangzhou RiboBio Co., Ltd. • Ingredient: SARS-COV-2 Delta and Omicron Variant's Spike protein mRNAs • Dose: 0.3ml RBMRNA-405 (60µg) • Route of administration: IM injection in lateral deltoid muscle of upper arm	• Product name: COMIRNATY ® (BNT162b2) • Manufacturer: Pfizer • Dose: 0.3m1 COMIRNATY ® (30µg) • Route of administration: IM injection in lateral deltoid muscle of upper arm • After the confirmation of your participation, you will be randomized in a ratio of I :1 to receive either • the investigational vaccine or the positive control.

iv. Details regarding IMPs & required quantity along with justification:

A. Active: COVID-19 mRNA Vaccine (RBMRNA-405)
Dosage Form: Injection.

B. Control: 0.3m1 COMIRNATY ® (30µg)
Dosage Form: Injection.

C. Quantity required:

Study Vaccine COVID-19 mRNA Vaccine (RBMRNA-405)

- Sponsor: Argorna Pharmaceuticals Co., Ltd
- Manufacturing: Guangzhou RiboBio Co., Ltd
- Specification: 1.0ml/vial; 0'2mg/ml (0'3ml each dose; one vial for three)
- Total no. of vaccine doses:750
- Total no. of vials for volunteers: 750/3: **250** vials
- Retention doses for archiving: 30
- Total no. of vials for retention: 30/3= 10 vials
- Total no. of vials for volunteers + Total no. of vials for retention=250+10=**260 vials**

Control Vaccine Comirnaty ® (BNT162b2)

- 0.3m1 each dose - 1 vial for five
- Total no. of vaccine doses: 750
- Total no. of vials for volunteers: 750/5: **150** vials
- Retention doses for archiving: 30
- Total no. of vials for retention: 30/5: 6 vials
- Total no. of vials for volunteers + Total no. of vials for retention = 150 + 6 = **156 vials**

v. Number of subjects to be recruited: **1500** Subjects

vi. Anticipated cost of the project: USD 1,500,000/-

vii. Study design & details:

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	1500 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Blinded (Participant)
Primary Purpose:	Treatment (Booster dose)
Official Title:	A Phase 3, Multi-Center, Randomized, Blind, Positive-controlled study to evaluate the immunogenicity and safety of COVID-19 mRNA Vaccine (RBMRNA-405) as a booster dose in Adults who completed 2 doses of inactivated vaccination

3. The study carried out under the supervision of Dr. Raza Shah (National-PI). The trial comprises of following objective(s);

A. Primary Endpoints

Immunogenicity

- Level of neutralizing antibody against SARS-CoV-2 (Omicron BA.1, etc.) at day 14 post booster vaccination;

Safety:

- Solicited local and systemic AEs within 14 days after booster vaccination;
- Unsolicited AEs within 28 days after booster vaccination;

B. Secondary Endpoints

Immunogenicity:

- Level of neutralizing antibody against SARS-CoV-2 (Omicron 8A.1, etc.) at day 28 post booster
- vaccination;
- Level of IgG antibody (ELISA) against SARS-CoV-2 (Omicron 8A.1, etc.) S protein at day 14, and day 28 post booster vaccination;

Safety:

- SAEs throughout 12 months after booster vaccination.

4. The details of the submitted documents are as under;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs. 200,000/- deposited vide challan no. 083606668, dated 11th November, 2022.
3	Investigator Brochure (s)	IB Version 3.1 dated 21st August, 2022 is attached IB of control product Comirnaty manufactured by Pfizer is not provided.
4	Final protocol	Attached Protocol No. CRO-011-VAC-(SARS-CoV-2 mRNA Phase III)-2022/Protocol/1.0 Version 1.0, dated 13th September, 2022 * Insurance policy details / procedure for trial related health injury compensation is need to be clarified & should be incorporated in trial protocol.
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.	The required quantity of IMPs is as follows: Study Vaccine COVID-19 mRNA Vaccine (RBMRNA-405) • Sponsor: Argorna Pharmaceuticals Co., Ltd • Manufacturing: Guangzhou RiboBio Co., Ltd • Specification: 1.0ml/vial; 0'2mg/ml (0'3ml each dose; one vial for three) • Total no. of vaccine doses:750 • Total no. of vials for volunteers: 750/3: **250** vials • Retention doses for archiving: 30 • Total no. of vials for retention: 30/3= 10 vials • Total no. of vials for volunteers + Total no. of vials for retention=250+10=**260 vials** Control Vaccine Comirnaty ® (BNT162b2) • 0.3m1 each dose - 1 vial for five • Total no. of vaccine doses: 750 • Total no. of vials for volunteers: 750/5: **150** vials • Retention doses for archiving: 30 • Total no. of vials for retention: 30/5: 6 vials

		• Total no. of vials for volunteers + Total no. of vials for retention = 150 + 6 = **156 vials**
9	Site of the trial	i. Center for Bioequivalence Studies and Clinical Research (CBSCR) ICCBS, University of Karachi, Pakistan. (CTS-0046) ii. Creek General Hospital Ibrahim Haidery, Korangi Creek, Karachi. (CTS-0077) iii. Pak International Hospital, D.H.A. Phase-I, Defense Housing Authority, Karachi. (CTS-0078)
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	i. Ref: # ICCBS/CBSCR/IEC/LET-051/2022, dated 11th October, 2022. (CBSCR-ICCBS) ii. Ref: # PIH/IRB LET-001/2022, dated 24th October, 2022. (Pak International Hospital, Karachi) iii. Ref: # CGH/Ethics/2022/27/10/318, dated 27th October, 2022. (Creek General Hospital, Karachi)
11	Approval of National Bio-ethics Committee (NBC)	Reference No.4-87/COVID-120/22/578, dated 07th November, 2022 (for a period of **Six** months).
12	CV's of the Investigators	CVs of following experts are attached. **v.** Prof. Dr. Muhammad Raza Shah (PI) (162-166/Corr.) **vi.** Dr. Naveed Yunus (Site-PI-CBSCR) (167-170/Corr.) **vii.** Dr. Muhammad Iqbal Afridi (Site-PI-Pak International Hospital, Karachi) (171-191/Corr.) **viii.** Prof. Dr. Farhat Bashir (Site-PI-Creek General Hospital, Karachi) (192-196/Corr.)
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Following documents are attached: i. Copy of DML of Guangzhou RiboBio Co., Ltd., China is attached ii. Batch Certificate for Investigational Product issued by manufacturer is attached. * GMP Certificate of IMP manufacturer is not provided. ** CoPP for control product COMIRNATY ® (BNT162b2) & GMP Certificate of its manufacturer: Pfizer is not provided.
14	Pre-clinical/clinical safety studies	Attached.
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.	750 Subjects in Study Group 750 Subjects in Control Group Total 1500 Subjects
19	Name of Monitors & Clinical Research Associate	Attached.
20	Evidence of registration in country of origin.	Copy of DML of Guangzhou RiboBio Co., Ltd., China is attached Batch Certificate for Investigational Product issued by manufacturer is attached. * GMP Certificate of IMP manufacturer is not provided. ** CoPP for control product COMIRNATY ® (BNT162b2) & GMP Certificate of its manufacturer: Pfizer is not provided.
21	Copy of registration letter (if registered in Pakistan)	Not applicable.
22	Sample of label of the investigational product / drug.	Attached only for test product, not provided for control product.
22	Duration of trial	**Twelve (12)** months.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings are recorded:

i. Investigator Brochure for control product (COMIRNATY ® Mfd by Pfizer) need to be provided.
ii. Insurance policy details / procedure for subject's insurance need to be clarified & should be incorporated in trial protocol.
iii. GMP Certificate of IMP manufacturer (M/s Guangzhou RiboBio Co., Ltd., China) is not provided.
iv. CoPP for control product (COMIRNATY ® (BNT162b2)) & GMP Certificate of its manufacturer (Pfizer) is not provided.
v. Sample label for control product (COMIRNATY ®) is need to be provided.

06. Accordingly, shortcomings letter was issued on 26th January, 2023.

07. Reply in response to this Division's letter even number dated 26th January, 2023 received from Dr. Raza Shah, General Manager, CBSCR, Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, University Road, Karachi, dated 30th January, 2023.

08. Summary of submitted reply along with attachments is as follows:

Sr. No.	Descriptions / Shortcomings	Reply	Remarks
i.	Investigator Brochure for control product (COMIRNATY ® Mfd by Pfizer) need to be provided.	**Attached**	---
ii.	Insurance policy details / procedure for subject's insurance need to be clarified & should be incorporated in trial protocol.	**Attached**	---
iii.	GMP Certificate of IMP manufacturer (M/s Guangzhou RiboBio Co., Ltd., China) is not provided.	**Public notice issued by China State Drug Administration body is attached with clarification regarding non-issuance of GMP Certificate**	GMP Certificate of IMP manufacturer is not provided
iv.	CoPP for control product (COMIRNATY ® (BNT162b2)) & GMP Certificate of its manufacturer (Pfizer) is not provided.	**Attached**	---
v.	Sample label for control product (COMIRNATY ®) is need to be provided.	**Attached**	---

09. After evaluation of the submitted reply following shortcomings observed:

i. It is submitted by applicant that China FDA is not issuing GMP after 2018 as their policy but it is a regulatory requirement, CSC may deliberate & discuss the matter to dispose of the case.

10. Accordingly, shortcomings letter was issued on 06th February, 2023, still response is awaited.

11. Further, Trial Protocol & other technical documents were shared through email to all CSC members for technical evaluation & expert opinion, but no comments received.

12. Secretary CSC presented the case before the Committee and Prof. Dr. Raza Shah also joined the meeting through Zoom. CSC suggested to include a clinician as Co-Principal investigator in the trial and same was agreed by the applicant / PI

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for further deliberations & submission of following points:

a. clarification regarding Phase-II Clinical & Safety Data for RBMRNA-405 by PI.
b. Inclusion of a Clinician in the trial as a Co-PI.

13. Accordingly, decision was communicated vide letter number F.No.16-38/2023-CSC dated 13th February, 2023.

14. In response to this Division's letter bearing number F.No.16-38/2023-CSC, dated 13th February, 2023, FR (Page 328 – 440/Corr.) (Attachment 10) is received from Dr. Raza Shah, General Manager, CBSCR, Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, University Road, Karachi, dated 15th February, 2023.

15. Applicant attached following documents;

i. Revised Protocol Version 2.0 (CRO-011-VAC-(SARS-CoV-2 RBMRNA Phase II/III)-2022/Protocol/2.0), February 9, 2023. (Page 332-390/Corr.)
ii. Approvals of IRBs for Revised Protocol Version 2.0 (Page 392/Corr.)
iii. Approvals of IRBs for Revised Protocol Version 2.0 (Page 393-390/Corr.)
    a. Creek General Hospital, Karachi, dated 17th February, 2023. (Page 393-394/Corr.)
    b. CBSCR-ICCBS, Karachi, Dated 16th February, 2023. (Page 395/Corr.)
    c. Pak-International Hospital, Karachi, Dated 16th February, 2023. (Page 396/Corr.)
iv. CVs of Co-PIs
    a. Dr. Muhammad Nasir (Co-PI CBSCR-ICCBS) (Page 398-414/Corr.)
    b. Prof Dr. Farhat Bashir (Co-PI Creek General Hospital) (Page 415-419/Corr.)
    c. Dr. Muhammad Iqbal Afridi (Co-PI Pak-International Hospital) (Page 420-440/Corr.)

16. Summary of submitted reply along with attachments is as follows:

i. Clarification regarding Phase-II Clinical & Safety Data for RBMRNA-405 by PI.
Response: (Page 329-330/Corr.)

The monovalent vaccine RBMRNA-176 was developed for wild virus strains, while RBMRNA-405 bivalent vaccine is used against Delta and Omicron mutant strains, using the same process, preparation and formula as 176, but with only a small change in the mRNA. Compared with the original wild virus strain, less than 2% of the nucleic acid sequences changed while more than 98% of the nucleic acid sequences remained the same. Therefore, although the mutant strain has changed, very little change occurred in the nucleic acid sequence, so that the physical, chemical and biology properties of the 176 vaccine and the 405 vaccine(s) are almost the same.

The immunogenicity data from in vivo studies in small animal models (i.e., mice), and from phase I clinical trial of the bivalent vaccine 405 (detailed in the Investigator's brochure) demonstrates the higher neutralizing capacity of bivalent vaccine 405 and the resulting increased sera levels of anti-S IgG antibodies against the Omicron BA.1 virus strain, in a dose dependent manner.

In accordance to the FDA guideline (Development and Licensure of Vaccines to Prevent COVID-19, Guidance for Industry, June 2020), page # 09 "*The totality of data for a specific COVID-19 vaccine candidate, including data from post-vaccination challenge studies in small animal models and from FIH clinical trials characterizing the type of immune responses induced by the vaccine will be considered in determining whether **Phase 3** studies can proceed in the absence of post-vaccination challenge data to address risk of ERD.*
and on ***Page # 10*** of this guideline it states that: *Initiation of late phase trials should be preceded by adequate characterization of safety and immunogenicity (e.g., in a few hundred participants for each vaccine candidate, dose level, and age group to be evaluated) to support general safety, potential for vaccine efficacy, and low risk of vaccine associated ERD. (enhanced respiratory disease).*

Results of non-clinical studies evaluating protection and/or histopathological markers of vaccine associated ERD following SARS-CoV-2 challenge and COVID-19 disease outcomes from earlier clinical development are other potentially important sources of information to support clinical trials with thousands of participants.

In accordance to the outcomes stated above, the Bivalent vaccine 405 was deemed suitable for a Phase III clinical trial as the safety and immunogenicity of both the parent vaccine (RBMRNA-176 and the modified vaccine (RBMRNA-405) has been established in early phase trials.

However, to overcome any ambiguity and to fulfil the usual pathway of drug approval process, we have modified the Title and Design of the protocol and included subjects for Phase II cohort.

ii. <u>Inclusion of a Clinician in the trial as a Co-PI.</u>

Response: (Page 330/Corr.)

We thank the honorable CSC members for considering the volunteers' health and suggestion to include a clinician as Co-Principal Investigator. Dr. Muhammad Nasir, Dr. Farhat Bashir, and Dr. Iqbal Afridi are designated as the Co-Principal Investigators for this Clinical Trial. Please find enclosed CVs of the Co-Principal Investigators attached herein for your record.

17. Applicant reply was also shared through email to all CSC members, no comments received. Protocol summary is as follows:

Protocol No.	CP-RBMRNA-405-005-III-PAK
Study Title	A phase II/III, multi-center, randomized, blind, positive-controlled study to evaluate the immunogenicity and safety of COVID-19 mRNA vaccine (RBMRNA-405) as a booster dose in adults who completed 2 doses of inactivated vaccination
Version No.	2.0
Version Date	February 9, 2023
Sponsor	Argorna Pharmaceuticals Co., Ltd.
Study Phase	Phase II/III
Indication	RBMRNA-405 is for active immunization to prevent COVID-19 caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) original and mutant strains (Omicron, etc.)
Study Population	Subjects aged 18 years old and above who have completed immunization with 2 doses of inactivated COVID-19 vaccine.
Sample Size	Phase II: **300** subjects will be enrolled. Phase III: **1500** subjects will be enrolled.
Study Vaccine	Study Vaccine: COVID-19 mRNA vaccine (RBMRNA-405) Specification: 1.0 ml/vial; 0.2 mg/ml (one vial for three) Formulation: Injection Storage and Transportation: Store and ship at 2~8°C, avoiding freezing. Positive Control: COMIRNATY Specification: One vial for five, 0.3ml each dose Formulation: Injection
Dosage and administration	0.3ml RBMRNA-405(60μg) or COMIRNATY (30μg) Intramuscular injection (IM) at upper arm deltoid on day 0
Study Objectives	Phase II: Primary Objective: To evaluate the safety of RBMRNA-405 vaccine as a booster dose against COVID-19 in adults who have completed 2 doses inactivated vaccination. Secondary Objectives: To evaluate the long-term safety and immunogenicity of a booster dose of RBMRNA-405 vaccine. Phase III: Primary Objective: To evaluate the immunogenicity and safety of RBMRNA-405 vaccine as a booster dose against COVID-19 in adults who have completed 2 doses inactivated vaccination. Secondary Objectives:

<table>
<tr><td></td><td>To evaluate the long-term safety and immunogenicity persistence of a booster dose of RBMRNA-405 vaccine.</td></tr>
<tr><td>Study Design</td><td>Overall Design:
The study includes a Phase II part and a Phase III part.
Phase II
The Phase II part is a randomized, blind and positive controlled clinical trial to evaluate the safety and immunogenicity of RBMRNA-405 as a booster dose in subjects aged 18 years old and above who have completed immunization with two doses of inactivated vaccine. A total of 300 subjects aged 18 years old and above who have completed immunization with two doses of inactivated vaccine will be recruited into this study. One booster dose of study vaccine or positive control vaccine are inoculated to the deltoid muscle of upper arm. The proportion of each group receiving the study vaccine or control vaccine is 1:1; 150 subjects will receive the
study vaccine and 150 subjects will receive positive control vaccine. The grouping of subjects is shown in the following table:
<table>
<tr><th>Group</th><th>Sample Size</th><th>Immunogenicity</th><th>Safety</th><th>Immunization program</th></tr>
<tr><td>Study Group</td><td>150</td><td rowspan="2">All subjects</td><td rowspan="2">All subjects</td><td rowspan="2">One booster dose on day 0 (minimum 6 months’ after completing the 2 doses of inactivated vaccine)</td></tr>
<tr><td>Control Group</td><td>150</td></tr>
</table>
A meeting of DSMB will be held to evaluate the safety of the phase-II clinical trial after 07 day of booster vaccination (i.e., RBMRNA-405 or positive control vaccine) of the last subject (i.e. 300th subject) enrolled in the trial. Thereafter, the DSMB will submit their recommendation for
the initiation of recruitment of phase-III clinical trial to PI and sponsor. After receiving recommendation from the DSMB the PI in consultation with sponsor will initiate the recruitment of the subjects in Phase III clinical trial and vice versa.
Safety:
 Safety observation within 28 days after booster vaccination All adverse events within 30 minutes after booster vaccination, solicited local and systemic adverse events within 0~14 days, and unsolicited adverse events within 0-28 days will be collected from all subjects.
 Long-term safety observation Collect all SAE, AESI and pregnancy events within 6 months after booster vaccination.
Immunogenicity:
 Immunogenicity observation within 28 days after booster vaccination
Venous blood samples for immunogenicity testing will be collected from 150 subjects from study group & control group, respectively at day 0 (pre-booster vaccination), day 14, and day 28 post booster vaccination, to evaluate the level of IgG antibody against SARS-CoV-2 S protein and neutralizing antibody against SARS-CoV-2 (Omicron BA.1, etc.).

Phase III
The Phase III part is randomized, blind, parallel positive controlled clinical trial to evaluate immunogenicity and safety of RBMRNA-405 as a booster dose in subjects aged 18 years old and above who have completed immunization with two doses of inactivated vaccine. A total of 1500 subjects aged 18 years old and above who have completed immunization with two doses of inactivated vaccine will be recruited into this study. One booster dose of study vaccine or positive control vaccine are inoculated to the deltoid muscle of upper arm. The proportion of each group receiving the study vaccine or control vaccine is 1:1; 750 subjects will receive the
study vaccine and 750 subjects will receive positive control vaccine. The grouping of subjects is shown in the following table:

<table>
<tr><th>Group</th><th>Sample Size</th><th>Immunogenicity</th><th>Safety</th><th>Immunization program</th></tr>
<tr><td>Study Group</td><td>750</td><td rowspan="2">All subjects</td><td rowspan="2">All subjects</td><td rowspan="2">One booster dose on day 0 (minimum 6 months’ after completing the 2 doses of inactivated vaccine)</td></tr>
<tr><td>Control Group</td><td>750</td></tr>
</table>
The safety of the study vaccine will be assessed by PI in the event that any suspension criteria will be triggered during the trial. The sponsor will decide whether to continue the trial after the “Recommendation" be provided by PI.
Immunogenicity:</td></tr>
</table>

	□ Immunogenicity observation within 28 days after booster vaccination Venous blood samples will be collected from 750 subjects from study group & control group, respectively at day 0 (pre-booster vaccination), day 14, and day 28 post booster vaccination, to evaluate the level of IgG antibody against SARS-CoV-2 S protein, and neutralizing antibody against SARS-CoV-2 (Omicron BA.1, etc.). □ Immune persistence observation Venous blood samples will be collected from subjects in study group at month 3 and month 6 post booster vaccination, to evaluate the level of IgG antibody against SARS-CoV-2 S protein. Safety: □ Safety observation within 28 days after booster vaccination All adverse events within 30 minutes after booster vaccination, solicited local and systemic adverse events within 0~14 days, and unsolicited adverse events within 0-28 days will be collected from all subjects. □ Long-term safety observation Collect all SAE, AESI and pregnancy events within 6 months after booster vaccination. Follow up plan of Phase II clinical trial: All subjects underwent 5 on-site visits to complete screening (visit 0), booster vaccination (visit 1), adverse event collection (visit 1, 2, 3, 4) and humoral immunization observation (visit 1, 3, 4). And site staffs may conduct telephone visit for subjects for long-term safety observation (visit 5, 6). And investigators may conduct the face-to-face or telephone visits for subjects according to actual needs, and make the follow-up records. Follow up plan of Phase III clinical trial: Positive control group subjects underwent 4 on-site visits to complete screening (visit 0), booster vaccination (visit 1), adverse event collection (visit 1, 2, 3) and humoral immunization observation (visit 1, 2, 3).6 on-site visits will be required for subjects in the study group to complete screening (visit 0), booster vaccination (visit 1), adverse event collection (visit 1, 2, 3), and long term safety observation (visit 4, 5), humoral immunization observation (visit 1, 2, 3), and immune persistence observation (visit 4, 5). And investigators may conduct the face-to-face or telephone visits for subjects according to actual needs, and make the follow-up records. Data Collection: Electronic Data Capture (EDC) system will be used to collect the necessary data for statistical analysis.
Study Endpoints	Phase II: Primary endpoints: □ Solicited local and systemic AEs within 7 days after booster vaccination □ Unsolicited AEs within 7 days after booster vaccination; Secondary endpoints: □ Solicited local and systemic AEs within 14 days after booster vaccination; □ Unsolicited AEs within 28 days after booster vaccination; □ Level of neutralizing antibody against SARS-CoV-2 (Omicron BA.1, etc.) at day 14, and day 28 post booster vaccination; □ Level of IgG antibody (ELISA) against SARS-CoV-2 (Omicron BA.1, etc.) S protein at day 14, and day 28 post booster vaccination; Exploratory endpoints for Phase II (study group): □ SAEs throughout 6 months after booster vaccination; Phase III: Primary endpoints: *Immunogenicity:* □ Level of neutralizing antibody against SARS-CoV-2 (Omicron BA.1, etc.) at day 14 post booster vaccination; *Safety:* □ Solicited local and systemic AEs within 14 days after booster vaccination; □ Unsolicited AEs within 28 days after booster vaccination; Secondary endpoints: *Immunogenicity:* □ Level of neutralizing antibody against SARS-CoV-2 (Omicron BA.1, etc.) at day 28 post booster vaccination; □ Level of IgG antibody (ELISA) against SARS-CoV-2 (Omicron BA.1, etc.) S protein at day 14, and day 28 post booster vaccination; *Safety:* Exploratory endpoints for Phase III (study group):

	□ Level of IgG antibody (ELISA) against SARS-CoV-2 (Omicron BA.1, etc.) S protein at month 3 and month 6 post booster vaccination. □ SAEs throughout 6 months after booster vaccination
Inclusion Criteria	The subjects must meet all of the following inclusion criteria: 1. Adults aged 18 years and older, able to provide legal proof of identity; 2. Participants voluntarily agreed to participate in the study and signed an informed consent form; 3. The subject has the ability to understand the research process and is willing and able to comply with all research proposals and other requirements of the study; 4. Able to cooperate to complete the 06 months' study follow-up. 5. Have received 2 doses of inactivated vaccination with the most recent dose minimum six months prior to enrolment, no other novel coronavirus vaccines are administered from the second dose of inactivated vaccine to the present study; 6. SARS-CoV-2 etiological testing (RT-PCR Assay) negative 7. Male and female subjects of childbearing age agree to use effective contraception from screening period until06 months after vaccination□ 8. Non-pregnant period (negative result of pregnancy test), non-lactation period; 9. Male and female subjects of child-bearing age agree that do not donate eggs (eggs, oocytes) for assisted reproduction (female subjects of reproductive age) or avoid sperm donation (male subjects) from screening period until 06 months after vaccination.
Exclusion Criteria	Subjects meeting any of the following exclusion criteria are not allowed to be enrolled: 1. Have received any COVID-19 vaccine other than 2 doses of the inactivated vaccine. 2. History of severe acute respiratory syndrome (SARS), severe acute respiratory syndrome coronavirus- 2 (SARS-CoV-2) or COVID-19, middle east respiratory syndrome (MERS) and other human coronavirus infections or disease. 3. The vital signs or physical examination are clinically significant abnormal as determined by the investigators in screening. 4. Fever (oral temperature ≥37.5°C) on the day of the vaccination; 5. A history of severe allergy (including drugs, vaccines, and foods) or to any component of the experimental vaccine, e.g., allergic shock, laryngeal edema, anaphylactoid purpura, dyspnea, and angioneurotic edema, etc. 6. Subjects have contraindications to intramuscular injection, such as having been diagnosed with thrombocytopenia, any blood clotting disorder, or receiving anticoagulant therapy; 7. Subjects have been diagnosed with a serious disease, congenital malformation or chronic disease (including but not limited to: respiratory disease or bronchitis such as asthma, serious cardiovascular disease, serious cerebrovascular disease, kidney disease, serious or uncontrollable diabetes, autoimmune disease, thrombocytopenic purpura, thalassemia, malignant tumor, hereditary allergic constitution, etc.) that may interfere with the conduct or completion of the study; 8. Diagnosed with diseases may affect immune system function, including malignant tumor, congenital or acquired immune deficiency or suppression (e.g., tuberculosis, human immunodeficiency virus (HIV)), Hepatitis B, hepatitis C, syphilis infection, uncontrollable autoimmune disease, no spleen or spleen dysfunction; 9. Medical history or family history of central nervous system disease, convulsions or tics, epilepsy, meningitis, neurological disorders, mental disorders, cerebritis, myelitis, Guillian-Barre syndrome, etc. 10. Long-term use of immune-potentiator or immunosuppressant therapy within 6 months prior to vaccination (continuous oral or injection for more than 14 days); 11. Use of any blood or blood-related products (e.g. blood transfusion, use of human albumin, human immunoglobulin, etc.) or have received solid organ or bone marrow transplantation within 3 months prior to vaccination; 12. Lymph node-related diseases (such as lymphadenitis, lymphaden adhesions, lymph node tuberculosis, tumor metastasis, etc.) or skin scars and fistulas at the lymph node site, or lymphadenopathy, tenderness, skin redness and swelling at the lymph node site within 7 days prior to vaccination. 13. Within 3 days prior to vaccination, an acute illness or attack of a chronic disease, or the use of antipyretic analgesic or anti-allergic drugs;

Decision: -

The CSC after detailed discussion and deliberation decided;

a. *To approve the Phase-II & Phase III of the Clinical Trial titled, "COVID-19 mRNA Vaccine (RBMRNA-405) as a Booster Dose in Adults Who Completed 2 Doses of Inactivated Vaccination" to be conducted at Center for Bioequivalence Studies and Clinical Research (CBSCR) ICCBS, University of Karachi, Pakistan. (CTS-0046) as per following design:*

- ***Phase-II***

Group	*Sample Size*	*Immunogenicity*	*Safety*	*Immunization program*
Study Group	*150*	*All subjects*	*All subjects*	*One booster dose on day 0 (minimum 6 months' after completing the 2 doses of inactivated vaccine)*
Control Group	*150*			

- ***Phase-III***

Group	*Sample Size*	*Immunogenicity*	*Safety*	*Immunization program*
Study Group	*750*	*All subjects*	*All subjects*	*One booster dose on day 0 (minimum 6 months' after completing the 2 doses of inactivated vaccine)*
Control Group	*750*			

b. *However, the applicant will submit Phase II safety data and Data Safety & Monitoring Board report after completion of Phase-II trial. The Chairman CSC will decide to permit to initiate Phase III or otherwise, after evaluation/ review of submitted Phase 2 data and DSMB report, accordingly.*

AGENDA ITEM XIV:

APPLICATION FOR APPROVAL OF PHASE-III CLINICAL TRIAL TITLED "AN ADAPTIVE, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE-III STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AEROSOLIZED NOVAFERON VS. PLACEBO IN NON-HOSPITALIZED ADULT PATIENTS WITH MILD COVID-19", FROM CBSCR-ICCBS, KARACHI. F. No.03-17/2022-DD (PS)

Application was from Dr. Raza Shah, General Manager, CBSCR, Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, University Road, Karachi, dated 12th August, 2022. 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. 3306333872, dated 26th July, 2022.

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

i. **Sponsor:** Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan District, Qingdao, Shandong Province, China.

ii. **Purpose of trial:** This is an adaptive, Multicenter, Randomized, Double-blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of aerosolized JH509 vs. Placebo in Non-Hospitalized Adult Patients with Mild COVID-19, Rate of severe conditions with Score 3 or more serious on a seven-point ordinal scale from the start date of investigational drug administration (Day 1) to Day 28. [Time Frame: 28 days]

iii. **Arms & Interventions:**

Arm(s)	**Intervention/treatment**
Active Comparator: Novaferon ® Inhaled Novaferon, given 20 µg BID, daily for 7 days	**Biological:** Novaferon ® (a novel recombinant antiviral protein drug) Recombinant Cytokine Gene Derived Protein
Placebo Comparator: Placebo Inhaled saline (placebo), given BID, daily for 7 days	**Biological:** Placebo (Saline)

iv. Details regarding IMPs & required quantity along with justification:

A. Active: Novaferon ® (a novel recombinant antiviral protein drug)

Dosage Form: Aerosol.

Composition: Recombinant Cytokine Gene Derived Protein.

Route: Inhalation.

B. Placebo: Saline

Dosage Form: Aerosol

Route: Inhalation.

C. Quantity required:

	Novaferon	**Placebo**
No. of dose per day	2+2=4 Vials	2+2=4 Vials
Total Dose (2-2 vials for 7 days)	4x7=28Vials+4 extra vials for backup 32 vials	
No. of Volunteers	111	111
Total no. of Investigational drugs to be dispensed	111x32 = 3552 Vials	111x32 = 3552 Vials
Retention Samples for archiving	3552 vials	3552 vials
Total no. of vials for patients * Retention Samples for archiving	3552 +3552=7104 Vials	3552 +3552=7104 Vials

v. Number of subjects to be recruited: **222** Subjects

vi. Anticipated cost of the project: USD 50,000/-

vii. Study design & details:

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	111 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Investigator)
Primary Purpose:	Treatment
Official Title:	An Adaptive, Multicenter, Randomized, Double-blind, Placebo-Controlled Phase III Study to Evaluate the Efficacy and Safety of Aerosolized JH509 vs. Placebo in Non-hospitalized Adult Patients With Mild COVID-19
Actual Study Start Date :	28th October, 2021
Estimated Primary Completion Date :	March, 2022
Estimated Study Completion Date :	June 2022

3. The study carried out under the supervision of Dr. Raza Shah (PI). The trial comprises of following objective(s);

A. Primary objectives: Rate of severe conditions with Score 3 or more serious on a seven-point ordinal scale from the start date of investigational drug administration (Day 1) to Day 28. [Time Frame: 28 days]

B. Secondary objective: To evaluate the safety of aerosolized JH509 in COVID- l9 patients.

4. The details of the submitted documents are as under;

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs. 200,000/- deposited vide challan no. 3306333872, dated 26th July, 2022 * Original fee challan (DRAP's Copy) need to be provided.
3	Investigator Brochure (s)	IB Version 2.0 dated 17th December is attached
4	Final protocol	Attached Protocol No. CRO-009-NOV-(JH509)-2022/Protocol/1.1 Version 1.1, dated 09th November, 2022 * Insurance policy details / procedure for trial related health injury compensation is need to be clarified & should be incorporated in trial protocol.
5	Informed consent and participant information sheet (Urdu to English)	Attached but following points need to be clarified * Details regarding Insurance firm/MoU need to be provided
6	List of participating countries	Hong Kong, China & Pakistan. * Details regarding other participating countries is not provided.
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.	The required quantity of IMPs is as follows: i. Novaferon® (7104 Vials) ii. Placebo (7104 Vials)
9	Site of the trial	i. Dow University Hospital, Karachi. ii. The Indus Hospital & Health Network, Karachi. iii. Creek General Hospital, Karachi.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Ref: # ICCBS/CBSCR/IEC/LET-048/2022 dated 07th March, 2022.
11	Approval of National Bio-ethics Committee (NBC)	Reference No.4-87/COVID-105/22/06, dated 07th July, 2022 (for a period of **Six** months).
12	CV's of the Investigators	CVs of following experts are attached. **ix.** Prof. Dr. Muhammad Raza Shah (PI) (266-267/Corr.)
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Following documents are attached: • Copy of GMP Certificate M/s Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan District, Qingdao, Shandong Province, China. • Copy of CoPP for Novaferon® (Recombinant cytokine gene derived protein injection) 10µg/1.0ml/vial, is attached. * GMP Certificate for M/s Emballages Spectrum Packaging Inc., 617 rue McCaffrey, Saint-Laurent,

		QC H4T 1N3, Canada & CoPP or other evident document issued by relevant regulatory body for placebo is not provided.
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Summary of Ibis not provided.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	111 Subjects * Details regarding subjects distribution among other countries involved in trial need to be provided.
19	Name of Monitors & Clinical Research Associate	Dr. Muhammad Imran, M/s Global Scientific R&D, Karachi (CRO) * There are two different CRO(s) involved in trial, which needs to be clarified that which CRO has been notified/engaged
20	Evidence of registration in country of origin.	Copy of CoPP for Novaferon® (Recombinant cytokine gene derived protein injection) 10µg/1.0ml/vial, is attached. Copy of translation & New Drug Certificate issued by China Food & Drug Administration. Copy of COA also attached
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	The treatment period with investigational drug during the trial is 07 days & follow up will be up to 28 days. The trial is expected to completed in **six (06)** months.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings were recorded:

i. Original challan (DRAP's copy) need to be provided.
ii. Summary of Investigator's Brochure is not provided.
iii. Insurance policy details / procedure for trial related health injury compensation is need to be clarified & should be incorporated in trial protocol.
iv. GMP Certificate for M/s Emballages Spectrum Packaging Inc., 617 rue McCaffrey, Saint-Laurent, QC H4T 1N3, Canada & CoPP or other evident document issued by relevant regulatory body for placebo is not provided.
v. Details regarding subject's distribution among other countries involved in trial need to be provided.
vi. There are following two different CRO(s) involved in trial, which needs to be clarified that which CRO has been notified/engaged by sponsor & evident document (agreement/letter) need to be provided.
vii. Further it is informed that, a trial with same title but with different Sponsor is also enlisted on U.S National Trial Registry with identification number NCT05172037 (https://www.clinicaltrials.gov/ct2/show/NCT05172037). **In this regard following clarification is need to be clarified:**
   a. *Is subject trial the same, which is enlisted on U.S. Trial Registry?*
   b. *Is M/s Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan District, Qingdao, Shandong Province, China involved in the trial as a Sponsor? Whereas as per US trial registry its Sponsor is M/s Genova Inc., Japan.*
   c. *Is there any connection between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan District, Qingdao, Shandong Province, China? Or M/s Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan District, Qingdao, Shandong Province, China is a subsidiary of M/s Genova Inc., Japan.*

d. Is Novaferon® also registered in the name of M/s Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan District, Qingdao, Shandong Province, China along with M/s Genova Inc., Japan.

06. Accordingly, shortcomings were communicated vide letter bearing even number dated 12th September, 2022.

07. Reply in reference to this Division letter received from Prof. Dr. Muhammad Raza Shah, General Manager, CBSCR, Dr. Panjwani Center for Molecular Medicine & Drug Research, International Center for Chemical & Biological Sciences, University of Karachi, dated 12th September, 2022.

08. Summary of submitted reply along with attachments was as follows:

Sr. No.	Descriptions / Shortcomings	Reply	Remarks
I	Original challan (DRAP's copy) need to be provided.	Please find the original Challan DRAP's Copy) provided with this response letter (Appendix-1,)	---
II	Summary of Investigator's Brochure is not provided.	Please find the Summary of Investigator's Brochure attached with this response letter (See Appendix-2,).	---
III	Insurance policy details / procedure for trial related health injury compensation is need to be clarified & should be incorporated in trial protocol.	The protocol states "Investigators shall take actions for getting insurance….." under section 15. Payment and insurance sub-section 15.3. According to ICH-GCP Clause 6.14: Financing and insurance, "Financing and insurance if not addressed in a separate agreement", shall be included in the protocol. We have a separate Insurance policy for the trial subjects (See Appendix 3). In addition, the ICF clearly mention, "The cost of treatment for drug related side effects will be covered by insurance company which is hired for this trial" under clause 12. Cost for participation. (See Appendix 3,)	---
IV	GMP Certificate for M/s Emballages Spectrum Packaging Inc., 617 rue McCaffrey, Saint-Laurent, QC H4T 1N3, Canada & CoPP or other evident document issued by relevant regulatory body for placebo is not provided.	Spectrum Packaging Inc., is engaged for packaging and distributing the IP (Novaferon) and placebo for countries excluding Japan where Genova's trial is ongoing. Spectrum Packaging Inc., has been	As claimed in the reply, authorization from M/s Genova Inc., Japan, in favor of M/s Spectrum Packaging Inc., Canada for packaging of IMPs (Placebo & Novaferon) need to be provided.

		inspected and certified by Health Canada (see Appendix-4)	
V	Details regarding subject's distribution among other countries involved in trial need to be provided.	The study in non-hospitalized mild COVID-19 patients is going to be conducted in Pakistan and Japan with 222 subjects in each country. Phase III trial on the same formulation i.e. Inhaled Novaferon (NOVATION-I) in Hospitalized Patients with Moderate to Severe COVID-19 patients has been approved in different countries including Turkey, Argentina Brazil, Colombia, South Africa and Chile.	Previously it was informed in the application that, the trial will be carried out in Hong Kong, China & Pakistan. Further, as claimed that, it is a different trial from NOVATION, another trial enlisted on U.S. Trial Registry with identifier number NCT05172037 & its Sponsor is M/s Genova Inc., instead of M/s Genova Biotech (Qingdao) Co. Ltd., China & as per updated record its completion date was June, 2022 & its only site was Tokyo Shinagawa Hospital, Tokyo, Japan. Clarification in this regard need to provided & link between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co. Ltd., China need to be explained.
VI	There are following two different CRO(s) involved in trial, which needs to be clarified that which CRO has been notified/engaged by sponsor & evident document (agreement/letter) need to be provided. M/s CBSCR-ICCBS, University of Karachi M/s Global Scientific R&D, Karachi (CRO)	Please find the Authorization letter from the sponsor attached with this response letter (See Appendix-5,).	Authorization from study sponsor M/s Genova Inc., Japan need to be provided.
VII	Further it is informed that, a trial with same title but with different Sponsor is also enlisted on U.S National Trial Registry with identification number NCT05172037 *(*https://www.clinicaltrials.gov/ct2/show/NCT05172037 *)*. **In this regard following clarification is need to be clarified:** *a. Is subject trial the same, which is enlisted on U.S. Trial Registry?* *b. Is M/s Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan*	a. Yes, it is the same trial and was registered in us Trial Registry b. Genova Biotech (Qingdao) co., Ltd is the wholly owned subsidiary of Genova Inc., and responsible for manufacturing Novaferon (IP) for the clinical trials sponsored by Genova Inc. In this regard, Genova Biotech (Qingdao) Co., Ltd	In previously answered reply it was explained that it is a different trial with title of NOVATION-I, further as claimed that, it is a different trial from NOVATION, another trial enlisted on U.S. Trial Registry with identifier number NCT05172037 & its Sponsor is M/s Genova Inc., instead of M/s

	District, Qingdao, Shandong Province, China involved in the trial as a Sponsor? Whereas as per US trial registry its Sponsor is M/s Genova Inc., Japan. *c. Is there any connection between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan District, Qingdao, Shandong Province, China? Or M/s Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan District, Qingdao, Shandong Province, China is a subsidiary of M/s Genova Inc., Japan.* *d. Is Novaferon® also registered in the name of M/s Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan District, Qingdao, Shandong Province, China along with M/s Genova Inc., Japan.*	should be considered as Sponsor as well. c. Genova Biotech (Qingdao) co., Ltd is the wholly owned subsidiary of Genova Inc. d. Yes, Novaferon is registered in the names of Genova Biotech (Qingdao) co" Ltd. And M/s Genova Inc. As these two companies are in the same group.	Genova Biotech (Qingdao) Co. Ltd., China & as per updated record its completion date was June, 2022 & its only site was Tokyo Shinagawa Hospital, Tokyo, Japan. Clarification in this regard need to provided & link between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co. Ltd., China need to be explained. Moreover, M/s Genova Biotech (Qingdao) Co., Ltd. China, may not be considered as Sponsor or manufacturer of the product until authorization is granted by M/s Genova Inc., Japan. As claimed that, Novaferon also registered in the name of M/s Genova Biotech (Qingdao) Co. Ltd., China then kindly provide its registration certificate, both form Japan PMDA & China.

09. After evaluation of the reply following shortcomings have been recorded:

i. As claimed in the reply, authorization from M/s Genova Inc., Japan, in favor of M/s Spectrum Packaging Inc., Canada for packaging of IMPs (Placebo & Novaferon) need to be provided.

ii. Previously it was informed in the application that, the trial will be carried out in Hong Kong, China & Pakistan & now it is replied that the trial will be carried out in Japan & Pakistan, clarification in this regard need to be submitted.

iii. Previously it was informed in the application that, the trial will be carried out in Hong Kong, China & Pakistan. Further as claimed in the reply that, it is a different trial from NOVATION, another trial enlisted on U.S. Trial Registry with identifier number NCT05172037 & its Sponsor is M/s Genova Inc., instead of M/s Genova Biotech (Qingdao) Co. Ltd., China & as per updated record its completion date was June, 2022 & its only site was Tokyo Shinagawa Hospital, Tokyo, Japan. Clarification in this regard need to provided & link between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co. Ltd., China need to be explained.

iv. Authorization for CRO from study sponsor M/s Genova Inc., Japan need to be provided.

v. In previously answered reply it was explained that it is a different trial with title of NOVATION-I, further as claimed that, it is a different trial from NOVATION, another trial enlisted on U.S. Trial Registry with identifier number NCT05172037 & its Sponsor is M/s Genova Inc., instead of M/s Genova Biotech (Qingdao) Co. Ltd., China & as per updated record its completion date was June, 2022 & its only site was Tokyo Shinagawa Hospital, Tokyo, Japan. Clarification in this regard need to provided & link between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co. Ltd., China need to be explained. Moreover, M/s Genova Biotech (Qingdao) Co., Ltd. China, may not be considered as Sponsor or manufacturer of the product until authorization is granted by M/s

Genova Inc., Japan. As claimed that, Novaferon also registered in the name of M/s Genova Biotech (Qingdao) Co. Ltd., China then kindly provide its registration certificate, both form Japan PMDA & China.

10. Accordingly after approval from competent authority, shortcomings communicated to the applicant vide letter bearing even number, dated 16th November, 2022 but still response is awaited.

11. It is submitted that, the subject application was placed before CSC in its 36th CSC meeting held on 21st November, 2022. The Committee decided the case as follows:

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of following shortcoming as per Form-II of the Bio-Study Rules, 2017:

i. *As claimed in the reply, authorization from M/s Genova Inc., Japan, in favor of M/s Spectrum Packaging Inc., Canada for packaging of IMPs (Placebo & Novaferon) need to be provided.*
ii. *Previously it was informed in the application that, the trial will be carried out in Hong Kong, China & Pakistan & now it is replied that the trial will be carried out in Japan & Pakistan, clarification in this regard need to be submitted.*
iii. *As claimed in the reply, it is a different trial from NOVATION, another trial enlisted on U.S. Trial Registry with identifier number NCT05172037 & its Sponsor is M/s Genova Inc., instead of M/s Genova Biotech (Qingdao) Co. Ltd., China & as per updated record its completion date was June, 2022 & its only site was Tokyo Shinagawa Hospital, Tokyo, Japan. Clarification in this regard need to provided & link between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co. Ltd., China need to be explained.*
iv. *Authorization for CRO from study sponsor M/s Genova Inc., Japan need to be provided.*
v. *In previously answered reply it was explained that it is a different trial with title of NOVATION-I, further as claimed that, it is a different trial from NOVATION, another trial enlisted on U.S. Trial Registry with identifier number NCT05172037 & its Sponsor is M/s Genova Inc., instead of M/s Genova Biotech (Qingdao) Co. Ltd., China & as per updated record its completion date was June, 2022 & its only site was Tokyo Shinagawa Hospital, Tokyo, Japan. Clarification in this regard need to provided & link between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co. Ltd., China need to be explained. Moreover, M/s Genova Biotech (Qingdao) Co., Ltd. China, may not be considered as Sponsor or manufacturer of the product until authorization is granted by M/s Genova Inc., Japan. As claimed that, Novaferon also registered in the name of M/s Genova Biotech (Qingdao) Co. Ltd., China then kindly provide its registration certificate, both form Japan PMDA & China.*
vi. *The CSC also raised the query regarding non-clinical background of the PI in the study. In this regard justification is sought regarding PI being the responsible person in a Clinical Research & yet not being a Clinician/Physician.*

2. The applicant is directed to provide requisite documents within 30 days positively, failing which the application is liable to be rejected.

3. Furthermore, the Committee decided to re-inspect the proposed site for verification of the facilities for Phase-I, II, III & IV & its status as a Primary, Secondary or Tertiary care facility. And the Committee delegated the power to the Chairman CSC for constitution of the inspection panel. The nominated expert panel report may be placed before CSC for information.

Accordingly, CSC decision was communicated on 25th November, 2022 vide letter bearing No.16-36/2022-CSC for fulfilment of shortcomings in the application.

12. Further, Trial Protocol & other technical documents were shared through email to all CSC members for technical evaluation & expert opinion, but no comments received.

13. Secretary CSC presented the case before the Committee and Prof. Dr. Raza Shah also joined the meeting through Zoom. CSC suggested to include a clinician as Co-Principal investigator in the trial and same was agreed by the applicant / PI

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment of following shortcomings:

i. *As claimed in the reply, authorization from M/s Genova Inc., Japan, in favor of M/s Spectrum Packaging Inc., Canada for packaging of IMPs (Placebo & Novaferon) need to be provided.*
ii. *Previously it was informed in the application that, the trial will be carried out in Hong Kong, China & Pakistan & now it is replied that the trial will be carried out in Japan & Pakistan, clarification in this regard need to be submitted.*
iii. *As claimed in the reply, it is a different trial from NOVATION, another trial enlisted on U.S. Trial Registry with identifier number NCT05172037 & its Sponsor is M/s Genova Inc., instead of M/s Genova Biotech (Qingdao) Co. Ltd., China & as per updated record its completion date was June, 2022 & its only site was Tokyo Shinagawa Hospital, Tokyo, Japan. Clarification in this regard need to provided & link between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co. Ltd., China need to be explained.*
iv. *Authorization for CRO from study sponsor M/s Genova Inc., Japan need to be provided.*
v. *In previously answered reply it was explained that it is a different trial with title of NOVATION-I, further as claimed that, it is a different trial from NOVATION, another trial enlisted on U.S. Trial Registry with identifier number NCT05172037 & its Sponsor is M/s Genova Inc., instead of M/s Genova Biotech (Qingdao) Co. Ltd., China & as per updated record its completion date was June, 2022 & its only site was Tokyo Shinagawa Hospital, Tokyo, Japan. Clarification in this regard need to provided & link between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co. Ltd., China need to be explained. Moreover, M/s Genova Biotech (Qingdao) Co., Ltd. China, may not be considered as Sponsor or manufacturer of the product until authorization is granted by M/s Genova Inc., Japan. As claimed that, Novaferon also registered in the name of M/s Genova Biotech (Qingdao) Co. Ltd., China then kindly provide its registration certificate, both form Japan PMDA & China.*
vi. *The CSC also raised the query regarding non-clinical background of the PI in the study. In this regard justification is sought regarding PI being the responsible person in a Clinical Research & yet not being a Clinician/Physician.*

2. Further, it is decided & agreed by PI that, he will include a Clinician in the trial as a Co-PI & provide details.

14. In response to this Division's letter bearing number F.No.16-38/2023-CSC, dated 13th February, 2023, FR (Page 501 – 647/Corr.) (Attachment 17) is received from Dr. Raza Shah, General Manager, CBSCR, Dr. Panjwani Center for Molecular Medicine and Drug Research, International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, University Road, Karachi, dated 15th February, 2023.

35. Summary of submitted reply along with attachments is as follows:

iii. *As claimed in the reply, authorization from M/s Genova Inc., Japan, in favor of M/s Spectrum Packaging Inc., Canada for packaging of IMPs (Placebo & Novaferon) need to be provided.*
Response:
M/s Spectrum Packaging Inc. was engaged for packaging the IMPs (Placebo & Novaferon) for different Novaferon Trials. Please see the agreement Copy Attached as Appendix-I. (Page 509-528/Corr.)

iv. *Previously it was informed in the application that, the trial will be carried out in Hong Kong, China & Pakistan & now it is replied that the trial will be carried out in Japan & Pakistan, clarification in this regard need to be submitted.*
Response:
It is confirmed that the trials on Novaferon in non-hospitalized patients are going to be conducted only in Pakistan and Japan. The Trial NCT05172037 is in progress in Japan and its interim analysis (un-published data) indicated that the administration of aerosolized JH509 (Novaferon) is relatively safe, and significantly enhanced the clinical improvement. These data demonstrated that administration of aerosolized JH509 (Novaferon) is effective for COVID-19 patients. Application for approval and registration of clinical trial in Pakistan is submitted to your esteemed office.

v. *As claimed in the reply, it is a different trial from NOVATION, another trial enlisted on U.S. Trial Registry with identifier number NCT05172037 & its Sponsor is M/s Genova Inc., instead of M/s Genova Biotech (Qingdao) Co. Ltd., China & as per updated record its completion date was June, 2022 & its only site was Tokyo Shinagawa*

Hospital, Tokyo, Japan. Clarification in this regard need to provided & link between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co. Ltd., China need to be explained.

Response:

There are various trials on this product which are either in progress or in the process of initiation in different countries with different aims and objectives. The sponsor is planning to conduct Novation Trial (NCT04 70815 8) in Japan in many centers on 385 Hospitalized Adult Patients with Moderate COVID-19. Our trial is going to be conducted on mild to moderate COVID-19 Non-Hospitalized patients. Novaferon trial Novation-1 (NCT04669015) is another Phase 3 trial sponsored by Genova Inc. to be carried out on 914 participants and was initially projected to complete in August, 2022. However, Novaferon trial (NCT04669015) is still ongoing.

Trial with identification No. NCT0517203 7 is conducting in Japan. Its estimated completion date was June, 2022. However, the study is still going on. The interim analysis results (un-published data) of this trial indicated that the administration of aerosolized JH509 (Novaferon) is relatively safe, and significantly enhanced the clinical improvement. These data demonstrated that administration of aerosolized JH509 (Novaferon) is effective for COVID-19 patients.

The Trial submitted to your esteemed office has the same study design as that of NCT05172037 and will be registered in DRAP's Clinical Trial Registry upon approval and registration with a different identification Number. Genova Inc., (http://www.genova.cn/company/js/) is a high-tech multinational

biopharmaceutical company founded by a team of Chinese overseas students, integrating technology, investment and management. It focuses on the R&D and industrialization of original new biological drugs, owns a world-leading biological new drug research and development center in North America (Cayman Islands; see Appendix-2) (Page 529-530/Corr.), and has established wholly-owned subsidiaries in Hong Kong, Beijing, and Qingdao, China. M/s Genova Biotech (Qingdao) Co. Ltd. Is the wholly-owned subsidiary of Genova Inc. and authorized to conduct study in Pakistan (See the attached Authorization Letter Appendix-3) (Page 531-532/Corr.).

M/s Genova Biotech (Qingdao) Co. Ltd., Is the wholly-owned subsidiary of Genova Inc., and authorized to conduct study in Pakistan (See the attached Authorization letter for M/s Genova Biotech (Qingdao) Co. Ltd., from Genova Inc., Appendix-3) and Authorization of M/s Genova Biotech (Qingdao) Co. Ltd., for the CRO (CBSCR, ICCBS) Appendix-4. (Page 533-534/Corr.)

vi. *Authorization for CRO from study sponsor M/s Genova Inc., Japan need to be provided.*

Response:

Novation-1 is the trial on this same drug (Novaferon) in hospitalized patients titled, "A Randomized, Double-Blind, Placebo-Controlled, Phase JI! Study to Evaluate the Safety and Efficacy of Aerosolized Novaferon + SOC vs. Placebo + SOC in Hospitalized Adult Patients with Moderate to Severe COVID-19". This Novation-1 trial is multi-center trial (https://clinicaltrials.gov/ct2/show/NCT04669015) and is conducting in various countries including Brazil, Chile, Colombia, Indonesia, Kenya, South Africa, Turkey, Canada, and many others.

The "Novation" Trial Official Title is "A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Aerosolized Novaferon vs. Placebo in Hospitalized Adult Patients with Moderate COVID-I 9" that is going to be conducted in Japan in many centers on 385 patients with identification: NCT04708158.

The Trial submitted to your esteemed office has the same study design as that of the Trial "NCT0517203 7" which is conducting in Japan. The interim analysis of this trial shows satisfactory safety and efficacy profile of the inhalational Novaferon. Our Trial will be registered in DRAP clinical Trial Registry upon approval and registration.

vii. *In previously answered reply it was explained that it is a different trial with title of NOVATION-I, further as claimed that, it is a different trial from NOVATION, another trial enlisted on U.S. Trial Registry with identifier number NCT05172037 & its Sponsor is M/s Genova Inc., instead of M/s Genova Biotech (Qingdao) Co. Ltd., China & as per updated record its completion date was June, 2022 & its only site was Tokyo Shinagawa Hospital, Tokyo, Japan. Clarification in this regard need to provided & link between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co. Ltd., China need to be explained. Moreover, M/s Genova Biotech (Qingdao) Co., Ltd. China, may not be considered as Sponsor or manufacturer of the product until authorization is granted by M/s Genova Inc., Japan. As claimed that, Novaferon also registered in the name of M/s Genova Biotech (Qingdao) Co. Ltd., China then kindly provide its registration certificate, both form Japan PMDA & China.*

Response:

M/s Genova Inc., is not a Japanese company. It is a Cayman Islands' (North America) based registered company (See appendix 2) and Genova Biotech (Qingdao) Co. Ltd., China is the wholly-owned subsidiary of Genova Inc. In addition, Genova Biotech (Qingdao) Co. Ltd., China is responsible for manufacturing Novaferon for use in China, and distribution of IPs (Novaferon) to Japan, Pakistan and all other countries. Genova Biotech (Qingdao) Co. Ltd., China is the Manufacturer of Novaferon (See **Appendix 5(Page 535-538/Corr.);** GMP certificate) and registration holder of Novaferon in China (See **appendix 6 (Page 539-541/Corr.);** New drug certificate). The Drug (Novaferon) is not registered in Japan; trials in Japan are underway for its emergency use authorization and registration.

viii. *The CSC also raised the query regarding non-clinical background of the PI in the study. In this regard justification is sought regarding PI being the responsible person in a Clinical Research & yet not being a Clinician/Physician.*

Response:

We appreciate the respected CSC members' comments and justification about the PI background. As per the FDA definition, "Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. "Sub investigator" includes any other individual member of that team."

According to ICH GCP E6 R2 Clause 4.3.1 "A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions". We have our own SOP (CB(CTU)021RD-08) "Delegation of responsibilities to Research Team during clinical trial" where the PI assigns duties to responsible and qualified Clinical investigators/ sub investigators (Physicians) and other team members. The Trial related medical (or dental) decisions are always the responsibilities of physician in our set-up. Moreover, the PI of this study i.e., Prof Dr. M Raza Shah has extensive experience in DRAP and NBC-approved clinical trials including clinical trials of COVID-19. The Pl of this study led the DRAP and NBC-approved Phase 1 clinical trial of the Sinopharm Vaccine in Pakistan and successfully completed.

In addition, the followings are the credentials of PI related to Clinical Research that reflects the clinical background of PI:

The PI of this study remained as Pl of DRAP and NBC approved Clinical Trial for the treatment of COVID-19 patients with traditional Chinese medicine, entitled "Multi-center, Randomized, Double Blind and Placebo Controlled Clinical Trial on the Efficacy and Safety of Jinhua Qinggan Granules (JHQG) for the Treatment of COVID-19 Patients" The trial is successfully completed and the results of the trial are published in leading international journal of high impact factor (Appendix-7(Page 542-560/Corr.). NBC letter, DRAP letter, Publication)

The Pl of this study also remained Pl the DRAP and NBC-approved clinical trial entitled "A Randomized, Double-blind, Positive-Controlled Study to Evaluate the Efficacy and Safety of Fuke Qianjin Capsule in Patients with Pelvic Inflammatory Diseases" (Appendix-8: NBC approval, DRAP approval) (Page 561-565/Corr.)

The PI of this study also remained Pl of the DRAP and NBC-approved clinical trial entitled "Randomized, Double-Blind, Placebo-Controlled, Non-inferiority Clinical Trial on the Efficacy and Safety of Houtou Jianweiling Tablet in the Treatment of Chronic Non-Atrophic Gastritis." (Appendix-9. NBC approval, DRAP approval) (Page 566-570/Corr.)

The Pl of this study has conducted more than 28 Bioequivalence and PK studies in healthy volunteers. The Bioequivalence (BE) studies are a type of Phase 1 clinical trial. In BE (Safety, Pharmacokinetic) studies comparative Safety and Pharmacokinetic of drug is evaluated in health volunteers. All the parameters that are needed for execution of Phase 1 (Safety, Pharmacokinetic, dose tolerability) clinical trial are practiced in true spirit in BE studies. A wealth of knowledge about the clinical trial can be gathered by conducting BE studies. GCP and GLP are practiced both in BE and Phase 1 studies of IND. (Appendix-10. List of BE/BE, PK studies and approvals conducted by Pl) (Page 571-610/Corr.)

The PI of this study has participated in several GCP and GLP training courses needed to act as Pl. (Appendix-11. Training certificates of PI). (Page 611-619/Corr.)

The PI of this study has published more than 200 research articles in the area of Drug Delivery and Nano medicine through which the Pl has gathered a wealth of knowledge about the clinical trials and interactions of the drugs with the human body and the response of the human body to Drug {Appendix-12.) (Page 620-624/Corr.)

The Pl of this study has also Published (with International Publisher Elsevier) four books in the area of Drug delivery which increased in the depth of understanding of PI about the drug interaction with the body and response of the body. The books are also available on Amazon and one of the books was declared the best book of the year (2017) by HEC. The title of the books {Appendix-13) (Page 625-629/Corr.) is given below i.e.

a. Lipid-Based Nano carriers for Drug Delivery and Diagnosis, Paperback ISBN:9780323527293
b. Nano carriers for Cancer Diagnosis and Targeted Chemotherapy Paperback ISBN: 9780128167731
c. Metal Nanoparticles for Drug Delivery and Diagnostic Applications Paperback ISBN: 9780128169605
d. Nano carriers for Organ-Specific and Localized Drug Delivery Paperback ISBN: 9780128210932

ix. *Further, it is decided & agreed by PI that, he will include a Clinician in the trial as a Co-PI & provide details.*

Response:

We have included Dr. Muhammad Nasir (MBBS, FCPS, NIC # 43105-3434214-1) as Co-PI in this Trial. Please see the curriculum vitae (CV) of Dr. Muhammad Nasir attached as Appendix-14. (Page 630-647/Corr.)

15. Applicant reply was also shared through email to all CSC members, no comments received.

16. Submitted for consideration of CSC.

Decision:

The CSC after detailed discussion and deliberation decided to approve the Clinical Trial titled, "An Adaptive, Multicenter, Randomized, Double-Blind, Placebo-Controlled Phase-III Study to

Evaluate the Efficacy and Safety of Aerosolized Novaferon Vs. Placebo in Non-Hospitalized Adult Patients with Mild COVID-19", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site(s) except Akram Medical Complex, Lahore:

i. *Dow University Hospital, Karachi.*
ii. *The Indus Hospital & Health Network, Karachi.*
iii. *Creek General Hospital, Karachi.*

2. A total of 111 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:

A. Active: *Novaferon ® (a novel recombinant antiviral protein drug)*
Dosage Form: *Aerosol.*
Composition: *Recombinant Cytokine Gene Derived Protein.*
Route: *Inhalation.*

B. Placebo: *Saline*
Dosage Form: *Aerosol*
Route: *Inhalation.*

C. Quantity required:

	Novaferon	***Placebo***
No. of dose per day	*2+2=4 Vials*	*2+2=4 Vials*
Total Dose (2-2 vials for 7 days)	*4x7=28Vials+4 extra vials for backup 32 vials*	
No. of Volunteers	*111*	*111*
Total no. of Investigational drugs to be dispensed	*111x32 = 3552 Vials*	*111x32 = 3552 Vials*
Retention Samples for archiving	*3552 vials*	*3552 vials*
*Total no. of vials for patients * Retention Samples for archiving*	*3552 +3552=7104 Vials*	*3552 +3552=7104 Vials*

AGENDA ITEM XV:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "A PHASE-II, RANDOMIZED, DOUBLE BLINDED STUDY, TO EVALUATE ABILITY OF THE PROBIOTIC VIVOMIXX TO IMPROVE ENVIRONMENTAL ENTEROPATHY IN PREGNANT WOMEN: A PROOF OF CONCEPT TRIAL IN BANGLADESH, PAKISTAN, SENEGAL, AND ZAMBIA", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-20/2022-CT (PS)

Application was received from Dr. Sayed Asad Ali, CNIC number: 42000-0501181-7, PI/Professor & Associate Dean, Department of Pediatric & Child Health, The Aga Khan University Hospital, Karachi, Pakistan, Stadium Road, Karachi dated 30th November, 2022. Wherein request has been made for approval of subject Clinical Trial. Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide challan no. 36062569, dated 17th November, 2022. The trial is also enlisted on U.S National Trial Registry with identification number ***NCT05501470*** *(https://clinicaltrials.gov/ct2/show/NCT05608928)*

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

i. **Sponsor:** Institut Pasteur de Dakar
ii. **Collaborators**:
   a. Bill and Melinda Gates Foundation
   b. International Centre for Diarrhoeal Disease Research, Bangladesh
   c. Aga Khan University
   d. University of Zambia

iii. **Purpose of trial:** Stunting in young children refers to attenuated linear growth. In the year 2020, 149.2 million children under the age of 5 were stunted, accounting for 22% of stunting globally. Stunting has short- and long-term consequences of increased morbidity and mortality, impairment of neurocognitive development, impaired responses to oral vaccines, and increased risk of non-communicable diseases. Stunting is partly driven by Environmental Enteric Dysfunction (EED), an enteropathic condition characterized by altered gut permeability, infiltration of immune cells and changes in villous architecture and cell differentiation. EED may help explain why nutritional supplementation either during pregnancy or early childhood has minimal value in correcting childhood stunting.

Probiotics may serve to overcome the problem of EED through all mechanisms of pathogenicity, by providing additional bacteria that may help in intestinal decolonization of pathogenic microorganisms (changing the microbiological niche), promoting epithelial healing, improving nutrient absorption, and restoration of an appropriate immune balance between tolerance and responsiveness.

This trial will explore the conceptual framework, that a well-known probiotic, that can improve the composition of the gut microbiota, can reduce biomarkers of intestinal inflammation and gut health. This will restore healthy microbial signaling to the host epithelium, ameliorate barrier function through secretion of mucus and antimicrobial factors, and improve nutrient availability.

iv. **Arms & Interventions:**

Arms	Interventions
Experimental: Vivomixx Participant in the treatment arm will receive a daily dose of the probiotic Vivomixx for 8 weeks.	Drug: VSL#3 VSL#3 (a mixture of Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus casei, Lactobacillus delbrueckii subspecies bulgaricus, Streptococcus salivarius subspecies thermophiles, Bifidobacterium breve, Bifidobacterium longum, and Bifidobacterium infantis), as VivomixxAll consenting participants will be randomized into the treatment to control arm, receiving either Vivomixx or a placebo for 8 weeks. During the study, women will visit the healthcare center on a weekly basis to receive sachets of Vivomixx or a placebo according to their trial arm. Other Name: Vivomixx Device: CapScan® The only non-standard sample collection instrument is the CapScan® device. The CapScan Collection Capsule ("Capsule") is a non-invasive device that collects gastrointestinal samples along the GI tract that are then analyzed outside the body. Samples collected by the Capsule will be expressed, then undergo DNA sequencing and mass spectrometric analysis to determine the identity and function of the bacterial and host cells in the different regions of the GI tract and compared to similar analyses conducted on concomitantly collected stool samples.
Placebo Comparator: Placebo Participant in the control arm will receive a daily dose of a placebo (microcrystalline cellulose) for 8 weeks.	Device: CapScan® The only non-standard sample collection instrument is the CapScan® device. The CapScan Collection Capsule ("Capsule") is a non-invasive device that collects gastrointestinal samples along the GI tract that are then analyzed outside the body. Samples collected by the Capsule will be expressed, then undergo DNA sequencing and mass spectrometric analysis to determine the identity and function of the bacterial and host cells in the different regions of the GI tract and compared to similar analyses conducted on concomitantly collected stool samples. Drug: Placebo The placebo for the experimental drug VSL#3 (Vivomixx) is microcrystalline cellulose. It is similar in appearance to VSL#3. Other Name: microcrystalline cellulose

v. Quantity of IMPs required along with justification:

IMP	Dosage Form	Strength	Pack Size	Total Quantity
Vivomixx Probiotic Blend (Lyophilised lactic acid bacteria and Bifidobacteria of eight different strains)	Sachet	450 billion CFU bacteria/sachet Weight:4.4 grams/ sachet	56 Sachets/ Envelope	38 Subjects 38x56:2128 Sachets*

Placebo (Microcrystalline Cellulose)	Sachet	Weight:4.4 grams/ sachet	56 Sachets/ Envelope	38 Subjects 38x56:2128 Sachets*

***** We will keep the margin of 20% in case of loss to follow up' so we will need total of 2553 sachets for each group.

There will be a subset of participants that will go through an evaluation of their gut microbiome using a device called "capscan". subject will sign consent prior to becoming part of this subset.

No. of participants	Consumption Per Participant	Total Quantity
40	4	160

a. Ancillary items with CapScan devices

S.No.	Items	Quantity
01	Stool collection containers with attachable lids	300
02	Stool collection tubes	172
03	Saliva collection kits	172
04	Snack bars	344
05	Hooked device retrieval wands	20
06	Device clamps	20
07	Individually wrapped tongue depressors for transferring stool to the collection tube.	172
08	1-hour timers	10
09	Sample return bags	150
10	Markers for writing info on stool collection lids	10

vi. Number of subjects to be recruited: 76 Subjects (Globally) 76 Subjects in Pakistan

vii. Anticipated cost of the project: USD 1,070,639/-

viii. Study design & details:

Study type	Interventional (Clinical Trial)
Estimated Enrollment :	76 participants (Globally)
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Care Provider, Investigator)
Masking Description:	Randomisation will be carried out using sealed envelopes, using a randomisation code prepared by the trial statistician, which will be stratified by study centre. Each woman who gives consent will be given a trial identification (TID) number which will match the number on the randomisation envelopes. The trial will be blinded with an identical placebo (microcrystalline cellulose, prepared by Mendes SA, Lugano). Samples will be run and analysed using TID only, with all data cleaning and re-assays carried out blinded. The trial statistician will unblind lab data once databases are finalised.
Primary Purpose:	Treatment
Official Title:	Ability of the Probiotic Vivomixx to Improve Environmental Enteropathy in Pregnant Women: a Proof of Concept Trial in Bangladesh, Pakistan, Senegal and Zambia
Estimated Study Start Date :	December, 2022
Estimated Primary Completion Date :	April, 2023
Estimated Study Completion Date :	October, 2023

3. The study will be carried out at mentioned sites comprising of following primary objective(s);

Site(s)

Primary Outcome Measures:

i. Change in inflammation and epithelial damage in pregnant women with environmental enteropathy [Time Frame: Day 0 (screening) - Day 56]
Percentage change (mean, unweighted) in a multiple panel of biomarkers between baseline and last sample collected after 56 days of treatment, compared to control group.

Secondary Outcome Measures:

i. Change in enteropathogen colonisation [Time Frame: Day 1 - Day 56]
Change in colonisation with specific enteropathogens (Salmonella, Shigella, Campylobacter, ETEC, EPEC, EAEC, rotavirus, norovirus, Giardia and Cryptosporidium), by qPCR, between baseline and last sample collected after 56 days of treatment, in Vivomixx compared to placebo groups

ii. Impact on the structure and function of the microbiome [Time Frame: Day 1 - Day 56]
Change in microbiome at community and composition level (as measured by whole-genome shotgun metagenomic sequencing, post versus pre-intervention), in the intervention and placebo groups

iii. Change in permeability [Time Frame: Day 1 - Day 56]
Change in LR ratio in Vivomixx compared to placebo groups

iv. Impact of the host metabolome in pregnant woman [Time Frame: Day 1 - Day 56]
Change in metabolome, measured by Nuclear Magnetic Resonance (NMR) spectroscopy in faecal and CAPSCAN samples before and after intervention

v. Rate of weight gain in the 2nd trimester of pregnancy [Time Frame: Day 0 (screening) - Day 56]
Weight gain velocity in the 2nd trimester of pregnancy

vi. Variability in endpoints across geographies and participating laboratories [Time Frame: Beginning of recruitment in the first study site - end of recruitment in the last study site (approximately 12 months)]
Measurements of variability, including standard deviations and kappa values; Preliminary work across all sites using identical kits and harmonised SOPs

Other Outcome Measures:

i. CapScan success rate in delivering an assessment of the microbiome [Time Frame: Day 1 and Day 56]
Recovery of useful data from CapScan; completion of whole gut microbiome profiles.

4. The details of the submitted documents are as under;

S. No.	Document	Remarks
i.	Application on prescribed Form-II	Attached
ii.	Prescribed Fee	Rs. 200,000/- deposited vide challan no. 36062569, dated 17th November, 2022.
iii.	Investigator Brochure (s)	Attached for IMP & Device Version 1.1, Dated: 14th February, 2022.
iv.	Final protocol	Attached Protocol No. MPIGH Version 1.0, dated 06th July, 2022 * Insurance details not described in trial protocol.
v.	Informed consent and participant information sheet (Urdu to English)	Attached. (English & Sindhi) * Urdu version of ICF also need to be developed ** Insurance details for subjects in case of any injury during the trail need to be included in consent form.
vi.	List of participating countries	Bangladesh, Senegal, Zambia, and Pakistan.
vii.	Phase of trial.	Phase – II
viii.	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.	Attached
ix.	Site of the trial	i. Matiari Research & Training Center, Matiari (Operated Under the Aga Khan University) (CTS-0035) * The Site Was Only Approved For EED-Clinical Device Trial Only, Applicant Need To Submitted Application For Approval Of The Proposed Site For Phase-II Clinical Trial

x.	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. IRB/ERC approval of **Aga Khan University Hospital**, **Karachi** dated 04th October, 2022 for a period of one year is attached.
xi.	Approval of National Bio-ethics Committee (NBC)	Approval reference letter No.4-87/NBC-850/22/493, dated 17th October, 2022 for a period of **One months** is attached.
xii.	CV's of the Investigators	CVs of following (PI & Co-PI) experts are attached. i. Dr. Sayed Asad Ali (PI) (Page 316-338/Corr.) ii. Umrani Fayyaz (Page 339-343/Corr.) iii. Najeeha Talat Iqbal (Page 344-373/Corr.) iv. Junaid Iqbal (Page 374-384/Corr.) v. Dr. Sheraz Ahmed (Page 385-389/Corr.) * Role in the study are not described.
xiii.	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following manufacturer(s) of IMP & Device used in the trial are not provided CoPP for IMP & Device to be used in the trial are not provided.
xiv.	Pre-clinical/clinical safety studies	Attached.
xv.	Summary of Protocol	Attached.
xvi.	Summary of Investigator Brochure	Attached.
xvii.	Adverse Event Reporting Form	Attached.
xviii.	No of patients to be enrolled in each center.	Number of patients to be enrolled: Total 76 subjects to be enrolled in Pakistan. Total 76 Subjects to be enrolled globally. * As it is a multi-country Clinical Trial so distribution of subject enrollments need to be described. As global enrolment mention on U.S. CTR is 76 and same number of enrolment mentioned for Pakistan.
xix.	Name of Monitors & Clinical Research Associate	Not provided.
xx.	Evidence of registration in country of origin.	**Not provided.**
xxi.	Copy of registration letter (if registered in Pakistan)	Not applicable.
xxii.	Sample of label of the investigational product / drug.	Not provided.
xxiii.	Duration of trial	06 months During23 Months December2022- November 2024.
xxiv.	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings are recorded:

i. Proposed Clinical trial site is not approved for Phase-II Clinical Trials. (The Site Was Only Approved for EED-Clinical Device Trial Only, Applicant Need to Submitted Application for Approval of the Proposed Site for Phase-II Clinical Trial)
ii. GMP certificate along with COPP & free sale certificate of the investigational product & Device to be used in the trial, are not provided.
iii. Evidence of registration in the country of origin for IMP & Device to be used in the trial, are not provided.
iv. Insurance details & compensation for subjects in case of any injury during the trial need to be included in Protocol & Informed Consent Form.
v. GMP Certificate(s) of manufacturer(s) of IMP & Device used in the trial are not provided
vi. CoPP for IMP & Device to be used in the trial are not provided.
vii. Evidence of registration in country of origin for IMP & Device need to be provided.
viii. As it is a multi-country Clinical Trial, so, distribution of subject enrollments among participating countries need to be described. As global enrolment mention on U.S. CTR is 76 and same number of enrolment mentioned for Pakistan.
ix. CVs of following experts are attached but their role in trial is not elaborated except of PI
    a. Dr. Sayed Asad Ali (PI)
    b. Umrani Fayyaz
    c. Najeeha Talat Iqbal

d. Junaid Iqbal
e. Dr. Sheraz Ahmed.

06. It is submitted that, subject application was placed before CSC in its 38th Meeting held on 08th February, 2023. The Committee decided the case as follows:

The CSC after detailed discussion and deliberation decided to defer the case for fulfilment of following shortcomings:

i. *Proposed Clinical trial site is not approved for Phase-II Clinical Trials. (The Site Was Only Approved for EED-Clinical Device Trial Only, Applicant Need to Submitted Application for Approval of the Proposed Site for Phase-II Clinical Trial)*
ii. *GMP certificate along with COPP & free sale certificate of the investigational product & Device to be used in the trial, are not provided.*
iii. *Evidence of registration in the country of origin for IMP & Device to be used in the trial, are not provided.*
iv. *Insurance details & compensation for subjects in case of any injury during the trial need to be included in Protocol & Informed Consent Form.*
v. *GMP Certificate(s) of manufacturer(s) of IMP & Device used in the trial are not provided*
vi. *CoPP for IMP & Device to be used in the trial are not provided.*
vii. *Evidence of registration in country of origin for IMP & Device need to be provided.*
viii. *As it is a multi-country Clinical Trial, so, distribution of subject enrollments among participating countries need to be described. As global enrolment mention on U.S. CTR is 76 and same number of enrolment mentioned for Pakistan.*
ix. *CVs of following experts are attached but their role in trial is not elaborated except of PI*
    f. *Dr. Sayed Asad Ali (PI)*
    g. *Umrani Fayyaz*
    h. *Najeeha Talat Iqbal*
    i. *Junaid Iqbal*
    j. *Dr. Sheraz Ahmed.*

2. It was also decided that, the proposed site will be inspected for verification of trial specific facilities & equipments. The CSC delegated its power to the Chairman CSC for constitution of inspection panel. Inspection report will be placed before CSC in its next meeting for consideration.

07. In response to this Division's letter bearing number F.No.16-38/2023-CSC, dated 13th February, 2023, FR (Page 480 – 505/Corr.) (Attachment 09) is received from Dr. Sayed Asad Ali, CNIC number: 42000-0501181-7, PI/Professor & Associate Dean, Department of Pediatric & Child Health, The Aga Khan University Hospital, Karachi, Pakistan, Stadium Road, Karachi dated 15th February, 2023.

08. Summary of submitted reply along with attachments is as follows:

i. *Proposed Clinical trial site is not approved for Phase-II Clinical Trials. (The Site Was Only Approved for EED-Clinical Device Trial Only, Applicant Need to Submitted Application for Approval of the Proposed Site for Phase-II Clinical Trial)*

Response:

Matiari Site was approved for clinical trials in August 2020 and approval is valid for three years (letter attached). ln this proof of concept study, we will collect data and laboratory samples collection at community level. Lab samples will be transported to Karachi on daily basis for analysis. Gestational ultrasound will be performed at Matiari centre and we have constructed separate space for this purpose and have procured ultrasound machine and have hired a sonologist. You are welcome to visit Matiari site anytime. We are just requesting you to expedite the approval process as other countries have already started enrollment.

ii. *GMP certificate along with COPP & free sale certificate of the investigational product & Device to be used in the trial, are not provided.*

Response:

Vivomixx is food supplement and is widely available for sell globally. It is available as over the counter and anybody can purchase it. The investigational Drugs (Vivomixx Active and Placebo Sachets) are manufactured at Premier Nutraceutical Pvt. Ltd. (PNPL) under an FSSAI manufacturing Licence (A copy of the licence is attached). The investigational drugs for this study are manufactured in a WHO-GMP facility. A copy of the GMP Certificate is attached; however, it was valid until 03-Feb-2023. The manufacturer (PNPL) has already submitted their application for renewal (copy attached) and the GMP Certificate would be issued after inspection

of the manufacturing facility. The old GMP Certificate would hold valid until the issuance of the new GMP Certificate. Please find attached the list of ingredients/probiotic strains approved by the FSSAI for manufacturing and marketing of probiotics as Food Supplements in India. For your ready reference, we have highlighted the strains that are present in the proprietary mix used for Vivomixx. It established the fact that Vivomixx is manufactured and regulated as a Food Supplement and we have GMP certificate. GMP certificate is expiring in this month and we have also attached renewal application. As it is food supplement so CoPP is not valid (see Vivomixx data sheet, GMP certificate, GMP renewal application). The CapScan devices are used only in clinical research studies approved by the respective institution's Ethics Committees (IRB, ERC). The devices are considered by the approving IRBs as non-significant risk devices and therefore do not require IDE approval in the USA. Furthermore, exporting the non-significant risk device for research clinical study can be considered permissible under FDA sections 801(e)(1). Justification is provided in annexure 13b.

iii. *Evidence of registration in the country of origin for IMP & Device to be used in the trial, are not provided.*

Response:

Evidence of registration of IMP provided (see attached). The CapScan devices are used only in clinical research studies approved by the respective institution's Ethics Committees (IRB, ERC). The devices are considered by the approving IRBs as non-significant risk devices and therefore do not require IDE approval in the USA. Furthermore, exporting the non-significant risk device for research clinical study can be considered permissible under FDA sections 801(e)(1).

iv. *Insurance details & compensation for subjects in case of any injury during the trial need to be included in Protocol & Informed Consent Form.*

Response:

All of our trial participants are covered under insurance (insurance email attached). Compensation details are provided in protocol section 21.0 and in trial consent is covered in possible risks and discomfort heading.

v. *GMP Certificate(s) of manufacturer(s) of IMP & Device used in the trial are not provided*

Response:

Vivomixx is food supplement and is widely available for sell globally. It is available as over the counter and anybody can purchase it. The investigational Drugs (Vivomixx Active and Placebo Sachets) are manufactured at Premier Nutraceutical Pvt. Ltd. (PNPL) under an FSSAI manufacturing Licence (A copy of the licence is attached). The investigational drugs for this study are manufactured in a WHO-GMP facility. A copy of the GMP Certificate is attached; however, it was valid until 03-Feb-2023. The manufacturer (PNPL) has already submitted their application for renewal (copy attached) and the GMP Certificate would be issued after inspection of the manufacturing facility. The old GMP Certificate would hold valid until the issuance of the new GMP Certificate. Please find attached the list of ingredients/probiotic strains approved by the FSSAI for manufacturing and marketing of probiotics as Food Supplements in India. For your ready reference, we have highlighted the strains that are present in the proprietary mix used for Vivomixx. it established the fact that Vivomixx is manufactured and regulated as a Food Supplement. The CapScan devices are used only in clinical research studies approved by the respective institution's Ethics Committees (IRB, ERC). The devices are considered by the approving IRBs as non-significant risk devices and therefore do not require IDE approval in the USA. Furthermore, exporting the non-significant risk device for research clinical study can be considered permissible under FDA sections 801(e)(1). Justification is provided in annexure 13b.

vi. *CoPP for IMP & Device to be used in the trial are not provided.*

Response:

CoPP is not applicable on both products. See explanation above.

vii. *Evidence of registration in country of origin for IMP & Device need to be provided.*

Response:

Evidence of registration for Vivomixx provided (see attached). The CapScan devices are used only in clinical research studies approved by the respective institution's Ethics Committees (IRB, ERC). The devices are considered by the approving IRBs as non-significant risk devices and therefore do not require IDE approval in the USA. Furthermore, exporting the non-significant risk device for research clinical study can be considered permissible under FDA sections 801(e)(1). Justification is provided in annexure 13b.

viii. *As it is a multi-country Clinical Trial, so, distribution of subject enrollments among participating countries need to be described. As global enrolment mention on U.S. CTR is 76 and same number of enrolment mentioned for Pakistan.*

Response:

Sample size is 76 each for all the contributing sites.

ix. *CVs of following experts are attached but their role in trial is not elaborated except of PI*

a. *Dr. Sayed Asad Ali (PI)*

b. *Umrani Fayyaz*
c. *Najeeha Talat Iqbal*
d. *Junaid Iqbal*
e. *Dr. Sheraz Ahmed.*

Response:
We have added details of their responsibilities in project in Annexures(attached).

Decision:

The CSC after detailed discussion and deliberation decided to approve the Clinical Trial titled, "A Phase-II, Randomized, Double Blinded Study, to Evaluate Ability of the Probiotic Vivomixx to Improve Environmental Enteropathy in Pregnant Women: A Proof of Concept Trial in Bangladesh, Pakistan, Senegal, and Zambia", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site:

i. *Matiari Research & Training Center, Matiari (Operated Under the Aga Khan University) (CTS-0035)*

2. A total of 76 Subjects will be enrolled in the study & following mentioned quantities of IMP & devices will be imported after getting necessary approval/NOC from concerned DRAP field office:

i.

IMP	***Dosage Form***	***Strength***	***Pack Size***	***Total Quantity***
Vivomixx Probiotic Blend (Lyophilised lactic acid bacteria and Bifidobacteria of eight different strains)	*Sachet*	*450 billion CFU bacteria/sachet Weight:4.4 grams/ sachet*	*56 Sachets/ Envelope*	*38 Subjects 38x56:2128 Sachets**
Placebo (Microcrystalline Cellulose)	*Sachet*	*Weight:4.4 grams/ sachet*	*56 Sachets/ Envelope*	*38 Subjects 38x56:2128 Sachets**

There will be a subset of participants that will go through an evaluation of their gut microbiome using a device called "capscan". subject will sign consent prior to becoming part of this subset.

No. of participants	***Consumption Per Participant***	***Total Quantity***
40	*4*	*160*

a. Ancillary items with CapScan devices

S.No.	***Items***	***Quantity***
01	*Stool collection containers with attachable lids*	*300*
02	*Stool collection tubes*	*172*
03	*Saliva collection kits*	*172*
04	*Snack bars*	*344*
05	*Hooked device retrieval wands*	*20*
06	*Device clamps*	*20*
07	*Individually wrapped tongue depressors for transferring stool to the collection tube.*	*172*
08	*1-hour timers*	*10*
09	*Sample return bags*	*150*
10	*Markers for writing info on stool collection lids*	*10*

AGENDA ITEM XVI:

DOSSIER SUBMISSION FOR THE CLINICAL TRIAL ENTITLED "HIP FRACTURE ACCELRATED SURGICAL TREATMENT AND CARE TRACK 2 (HIPATTACK-2) TRIAL". (F. **No.03-08/2023-DD (PS))**

The case is an application from Dr. Aamer Nabi Nur, CNIC No.61101-5442534-3, Consultant Orthopedic Surgeon, Shifa International Hospital Limited, Sector H-8/4, Islamabad, wherein request has been made for approval of Clinical Trial titled as "HIP fracture Accelerated Surgical TreaTment And Care track 2(HIP ATTACK-2) Trial". Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide slip number 4370984754, dated 6th January, 2022. The trial is also enlisted on U.S National Trial Registry with identification number NCT04743765

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

i. **Sponsor:** **Population Health Research Institute Hamilton General Hospital Campus, DBCVSRI**
237 Barton street East, Hamilton, Ontario, Canada L8L 2X2.

Brief Summary: The HIP ATTACK-2 trial is a multicentre, international, parallel group randomized controlled trial to determine whether accelerated surgery for hip fracture in patients with acute myocardial injury is superior to standard care in reducing death at 90 days after randomization. The trial will also assess secondary outcomes at 90 days after randomization: inability to independently walk 3 meters, time to first mobilization (first standing and first full weight bear), composite and individual assessment of major complications (e.g., mortality, non-fatal myocardial infarction, acute congestive heart failure, and stroke), delirium, length of stay, pain, and quality of life.

Number of subjects to be recruited: 1,100 Subjects (Globally)
Anticipated cost of the project: 500 CAD per patient/-
Study design & details:

Study Type	Interventional (Clinical Trial)
Estimated Enrollment :	1,100 participants (Globally)
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Single (Outcome Assessor)
Primary Purpose:	Treatment
Official Title:	HIP Fracture Accelerated Surgical TreaTment And Care tracK 2 (HIP ATTACK-2) Trial

5. The study will be carried out at mentioned sites comprising of following primary objective(s);

Site(s)	PI	Specialty	Phase of trial	Remarks
Shifa International Hospitals Ltd, Islamabad	Dr. Aamer Nabi Nur)	Consultant Orthopedic Surgeon	Phase-III	---

Study Objectives

iv. To determine whether accelerated surgery for Hip Fracture in patients with acute myocardial injury is superior to standard care in reducing death at 90 days after randomization.

6. The details of the submitted documents are as under;

S. No.	Document	Remarks

1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs. 200,000/- deposited vide slip number 4370984754, dated 6th January, 2022
3	Investigator Brochure (s)	**Surgical Trial. No IMP involved.**
4	Final protocol	Attached Protocol No. HIP ATTACKL-2 Version 1.0, dated 21.01.2021
5	Informed consent and participant information sheet (Urdu to English)	Attached.
6	List of participating countries	25-30 countries. Canada, USA, Mexico, Belgium, Denmark, Finland, Italy, Netherlands, Poland, Spain, United Kingdom, South Africa, Saudi Arabia, Chili, Australia, Hong Kong, India, Nepal, Malaysia, Pakistan.
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.	**Surgical Trial**
9	Site of the trial	**Site(s)** **PI** **Shifa International Hospitals Ltd, Islamabad** Dr. Aamer Nabi Nur-PI
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached.
11	Approval of National Bio-ethics Committee (NBC)	NBC approval reference letter No.4-87/NBC-872/22/453
12	CV's of the Investigators	CVs of Dr. Aamer Nabi Nur attached. following (PI & Co-PI) experts are attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	No IMP involved.
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	No IMP involved.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	**1-2 patient per month in each center. Not mentioned for Pakistan.**
19	Name of Monitors & Clinical Research Associate	1. Dr. Tehreem Zahid 2. Dr. Sundus Dadan 3. Dr. Palwsha Alvi 4. Raja Waseem Akram All are employees of Shifa International Hospital, Islamabad.

20	Evidence of registration in country of origin.	**No IMP involved.**
21	Copy of registration letter (if registered in Pakistan)	**Not applicable.**
22	Sample of label of the investigational product / drug.	**No IMP Involved.**
22	Duration of trial	48 Months
23	Undertaking on Stamp paper	Attached.

The case is about clinical trial is accelerated surgery for hip fracture in patients with acute myocardial injury is superior to standard care in reducing death at 90 days after randomization. This does not involve any IMP. Rule 1 of Bio-Study Rules, 2017 is reproduced as follows;

1. **Short title and commencement. -** (1) These rules may be called the Bio-study Rules, 2017.
(2) They shall apply to all contract research organizations, laboratories for clinical research, bio-availability and bio-equivalence study centers or organizations operating in public or private sector, involved in clinical trials of therapeutic goods and bio-availability or bio-equivalence studies on human subjects.
(3) They shall come into force at once.

Decision: -

The CSC after detailed discussion and deliberation deferred the case for following queries from the applicant.

i. to submit relevant provisions of the Bio Study Rules, 2017 under which subject trial/ study has been applied and CSC is competent to decide the subject trial.
ii. to submit the approvals of the trial in other countries, if any, as it is multi-country trial.

The applicant has submitted reply dated 22.02.2023 wherein he has stated that in response to DRAP queries on the trial applications, after reviewing the bio-study rules 2017 we found that HIP ATTACK does not meet the definition of Clinical Trial Outline by the DRAP. According to our interpretation, as the study is an interventional clinical trial without any interventional product that approval is subject to your adjudication. We would appreciate if you could provide us some clarification a terminate our application if it is not under Bio-Study Rules, 2017.

Decision:

The CSC after detailed discussion acceded to the request of the applicant to withdraw the trial titled, "HIP FRACTURE ACCELRATED SURGICAL TREATMENT AND CARE TRACK 2 (HIPATTACK-2) TRIAL"

***Meeting ended with vote of thanks to & from the Chair. ***