# MINUTES OF 38TH MEETING OF CSC HELD ON 08th FEBRUARY, 2023.

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38th meeting of Clinical Studies Committee was held on 08th 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. | **Prof. Dr. Saeed Ahmad Khan** | Professor of Medicine Bolan Medical College Quetta presently serving as head | Member |
| 4. | **Dr. Mirza Tasawer Baig.** | Associate Professor in the Department of Pharmacy Practice, Faculty of Pharmacy, | Member |
| 5. | **Dr. Faiza Bashir** | Nominee of Chairman, Pakistan Health Research Council, Islamabad. | Member |
| 6. | **Mr. Waqas Latif** | Data Analyst/Biostatistician in Quality Enhancement Cell (QEC) at University of | Member |
| 7. | **Ahsan Ul Haq Athar** | Deputy Director-II, Pharmacy Services Division-DRAP. | Secretary/Member |

2. Mr. Waqas Latif joined the meeting online through zoom link. Mr. Shafqat Hussain Danish, Assistant Director (PS) assisted the Secretary in presentation of the agenda.

**AGENDA ITEM I:**

**CONFIRMATION OF THE MINUTES OF THE 37TH CLINICAL STUDIES COMMITTEE'S MEETING.**

The minutes of the 37th CSC meeting were shared with all CSC members through email also. All CSC members submitted their consent & no comments/queries were received from the members. Accordingly, decisions of the meeting were communicated to the concerned. Minutes are placed again for confirmation/signatures of the members for confirmation.

2. Submitted for consideration & signatures of CSC members, please.

**Decision: -**

*The Clinical Studies Committee (CSC) deliberated and decided that as draft minutes are communicated to members via email for their comments so there is no need for their signature on the minutes. Minutes will be approved by the Chairman after comments by members (if any) and will be signed by Chairman and Secretary accordingly.*

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**AGENDA ITEM II:**

**DELEGATION OF POWER TO CHAIRMAN CSC BY THE COMMITTEE FOR CONSTITUTION OF INSPECTION PANEL & NOMINATIONS OF CO-OPTED MEMBERS IN CLINICAL STUDIES COMMITTEE UNDER THEBIO-STUDY RULES,2017.**

It is submitted that, following are some of the CSC functions:

*13 (4) (c) inspection of the premises prior to grant of license, approval of clinical trial, BA or BE study and during and after the completion of the trial or study, if so desired, by a panel constituted by the CSC and any co-opted member under sub-rule (6) of rule 13, any site where clinical trial and BA or BE study is planned to be conducted, to satisfy itself of the observance of conditions, guidelines or criteria as notified by the DRAP;*

*13(5) The CSC may constitute a sub-committee for the performance of any of its functions*

02. Further, Under the Rule 13(9) the CSC may delegate any of its powers to Chairman of the Committee in writing with appropriate justification

03. Accordingly, it was suggested that, the CSC may discuss the matter & may delegate its powers to the Chairman CSC to constitute inspection panel for quick disposal & may nominate Co-opted members to strengthen the Committee, the Committee may utilize expertise of Co-opted members in evaluation of technical documents & may utilize them in pre/post inspection of Clinical Trial Sites, CROs, Bio-analytical Laboratories & BA/BE Studies Centers.

**Decision: -**

*The CSC 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.*

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**AGENDA ITEM III:**

**A RANDOMIZED, DOUBLE BLINDED, PLACEBO-CONTROLLED PHASE II/III CLINICAL TRIAL TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF RECOMBINANT SARS-CoV-2 VACCINE (CHO CELL) LYB001 AS BOOSTER VACCINATION IN ADULTS ≥ 18 YEARS OF AGE OR OLDER COMPLETED 2 DOSE OR 3 DOSES OF INACTIVATED COVID-19 VACCINE. (F. No.03-22/2022-DD (PS))**

The case is an application from Dr. Ejaz Ahmad Khan, CNIC No.61101-6851424-9, Consultant Pediatrician, Shifa International Hospital Limited, Sector H-8/4, Islamabad, dated 15th 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 slip number 09276054633, dated 15th November, 2022. The trial is also enlisted on U.S National Trial Registry with identification number NCT05602558

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

i. **Sponsor:** Yantai Patronus Biotech Co., Ltd., China.
**Guangzhou** Patronus Biotech Co., Ltd., China

**Brief Summary:** The study will be conducted in two phases using a randomized, double-blind, placebo-controlled design. A phase II trial will be initiated to assess the safety of LYB001 as booster shots, and then proceed to a phase III trial to assess the vaccine efficacy (VE) of LYB001 against COVID-19 after an acceptable safety profile, per the judgement of Data and Safety Monitoring Board (DSMB), within 28 days after booster in the phase II trial is assessed. After collection of 155 COVID-19 cases, all participants will get unblinded. Participants assigned to the placebo group can choose to receive LYB001 vaccine at their own discretion.

**Phase II stage:**

The purpose of phase II study is to assess the safety of healthy subjects aged 18 years and older who have completed two-dose or three-dose inactivated COVID-19 vaccine for 6-18 months. About 200 age s-stratified subjects aged over 18 years will be randomly assigned to receive the LYB001 or placebo in a 1:1 ratio in the deltoid muscle of the upper arm.

The Phase III study will be initiated after the DSMB confirm that all subjects in Phase II experience acceptable safety profile within 28 days after booster. All subjects in Phase II trial will be required to complete efficacy follow-ups for 12 months along with safety observation, and will be included in the Phase III efficacy analysis set (Phase II data will eventually be combined with Phase III data for statistical analysis, including efficacy and safety data).

**Phase III stage:**

A total of 17800 participants aged 18 years and older who have completed two-dose or three-dose inactivated COVID-19 vaccine for 6-18 months. The participants will be randomly assigned to the LYB001 booster or placebo booster group in 1:1 ratio according stratification factors of study center and age (18-59 years vs. ≥60 years) , with participants aged ≥ 60 years accounting for over 20 percent of total population.

After booster vaccination, all subjects will be evaluated for protective efficacy and safety, and 1000 subjects (800 subjects aged 18-59 years, and 200 subjects aged ≥60 years) will be enrolled in the subgroup for immunogenicity evaluation (LYB001: Placebo=1:1).

All subjects will be followed up to 12 months after booster vaccination. The entire clinical study will be completed after the pre-defined COVID-19 cases has been achieved and each participant has completed 12-month follow-ups.

**ii. Study Vaccine/IMPs required along with justification:**

| Intervention name | LYB001 | Placebo |
|---|---|---|
| **Sourcing** | Yantai Patronus Biotech Co., Ltd., China | Yantai Patronus Biotech Co., Ltd., China |
| **Specification** | 30 ul0.5ml/Vial | 0.5mI/Vial |
| **Main ingredients** | The antigen consists of receptor-binding domain (RBD) from wild-type SARSCoV-2 displaying on virus like particle (VLP) vector, adjuvanted with aluminium hydroxide. | Aluminium hydroxide adjuvant |
| **Formulation** | Injection | Injection |
| **Dose regimen and route of administration** | Intramuscular injection (IM) at upper arm deltoid on day 0 | Intramuscular injection (IM) at upper arm deltoid on day 0 |
| **Storage** | 2-8oC away from light, avoiding freezing | 2-8oC away from light, avoiding freezing |
| **Batch number and expiration date** | To be determined | To be determined |

**iii. Quantity of IMPs required along with justification:**

| Study Intervention | Test Drug | Comparator |
|---|---|---|
| **Intervention Name** | LYB001 | Placebo |
| **Dose Formulation** | Injection | Injection |
| **Each Vial Contain** | 30 µg/0.5ml/Vial | 0.5ml/Vial |
| **Quantity to be imported** | 9450 | 9450 |
| **Total subjects to be recruited in Pakistan** | 18000 | |

**iv. Source of Investigational Medical Products (IMPs):**

- China

**v. Anticipated cost of the project:** USD 7270073/-

**vi. Study design & details:**

| | |
|---|---|
| Study Design | Interventional (Clinical Trial) |
| Estimated Enrollment : | 18,000 participants (Globally) |
| Allocation: | Randomized |
| Intervention Model: | Parallel Assignment |
| Masking: | Double (Participant, Investigator) |
| Primary Purpose: | Prevention |
| Official Title: | A Multicentre, Randomized, Double-blinded, Placebo-controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of Recombinant SARS-CoV-2 Vaccine (CHO Cell) LYB001 as Booster Vaccination in Adults 18 Years of Age or Older. |

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. Ejaz Ahmed Khan (National-PI) | Pediatric Infectious Diseases | Phase-II & III | --- |

| | | | | |
|---|---|---|---|---|
| **Al-Shifa Trust Research Center, Rawalpindi.** | Dr. Ume Sughra, Site-PI | Epidemiologist | Phase-III | --- |
| **Central Park Teaching Hospital, Lahore** | Prof. Dr. Muhammad Ahmad, Site-PI | Pulmonologist | Phase-III | |
| **Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad** | Prof Dr Tanwir Khaliq, Site-PI | General surgeon | Phase-III | |
| **Indus Hospital and Health Network, Karachi** | Dr. Faridah Amin, Site-PI | Family Medicine and Health sciences | Phase-III | |
| **Central Hospital, Gujranwala** | Dr.Salman Athar, Site-PI | Anesthesiologist | Phase-III | |
| **Avicenna Hospital & Medical College Lahore** | Dr. Waheed Ahmad, Site-PI | General Medicine | Phase-III | |
| **National Hospital and Medical Centre, Lahore** | Prof. Dr Muhammad Ishaque, , Site-PI | ENT specialist | Phase-III | Not approved as a generalized trial site for Phase-III CT |

Primary & Secondary Objectives

i. To assess the efficacy of a booster dose of LYB001 against symptomatic COVID-19 in participants 18 years of age or older completed two-dose or three-dose inactivated COVID-19 vaccine without evidence of past SARS-CoV-2 infection.
ii. To assess the efficacy of a booster dose of LYB00l against confirmed severe, critical COVID-19, and COVID-19 associated death in participants I 8 years of age or older completed two-dose or three-dose inactivated COVID-1 9 vaccine without evidence of past SARS-CoV-2 infection.
iii. To assess the immunogenicity profile of a booster dose of LYB001 in a subgroup of the participants l8 years of age or older completed two-dose or three-dose inactivated COVID-l 9 vaccine without evidence of past SARS-CoV-2 infection.

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 09276054633, dated 15th November, 2022 |
| 3 | Investigator Brochure (s) | Version 1.0, Dated: 08th August, 2022 is attached. |
| 4 | Final protocol | Attached<br>Protocol No. LYB001 /CT: PAK-301<br>Version 2.0, dated 08th October, 2022 |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached. |
| 6 | List of participating countries | **Pakistan only.** |
| 7 | Phase of trial. | Phase – II<br>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. | **Test Drug** LYB001 Injection 30 µg/0.5ml/Vial =9450<br>**Placebo** 0.5ml/Vial=9450 |
| 9 | Site of the trial | **Site(s)** — **PI**<br>**Shifa International Hospitals Ltd, Islamabad** — Dr. Ejaz Ahmed Khan (National-PI)<br>**Al-Shifa Trust Research Center, Rawalpindi.** — Dr. Ume Sughra, Site-PI<br>**Central Park Teaching Hospital, Lahore** — Prof. Dr. Muhammad Ahmad, Site-PI |

| | | |
|---|---|---|
| | | **Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad** Prof Dr. Tanwir Khaliq, Site-PI<br>**Indus Hospital and Health Network, Karachi** Dr. Faridah Amin, Site-PI<br>**Central Hospital, Gujranwala** Dr. Salman Athar, Site-PI<br>**Avicenna Hospital & Medical College Lahore** Dr. Waheed Ahmad, Site-PI<br>**National Hospital and Medical Centre, Lahore** Prof. Dr. Muhammad Ishaque, , Site-PI<br>**The National Hospital is not generalized approved trial site.** |
| 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/COVID-119/22/552, dated 28th October, 2022. |
| 12 | CV's of the Investigators | CVs of following (PI & Co-PI) experts are attached.<br>i. Dr. Ejaz Ahmed Khan (National-PI) Shifa International Hospital, Islamabad (187-206/Corr.)<br>ii. Dr. Ume Sughra, Site-PI (Al-Shifa Eye Trust Research Center, Rawalpindi) (208-223/Corr.)<br>iii. Prof. Dr. Muhammad Ahmad, Site-PI Central Park Teaching Hospital, Lahore (224-233/Corr.)<br>iv. Prof Dr. Tanwir Khaliq, Site-PI, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad (234-245/Corr.)<br>v. Dr. Faridah Amin, Site-PI, Indus Hospital and Health Network, Karachi (246-263/Corr.)<br>vi. Dr. Salman Athar, Site-PI, Central Hospital, Gujranwala (264-274/Corr.)<br>vii. Dr. Waheed Ahmad, Site-PI, Avicenna Hospital & Medical College Lahore (275-281/Corr.)<br>viii. Prof. Dr. Muhammad Ishaque, Site-PI, National Hospital and Medical Centre, Lahore. (282-287/Corr.) |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | GMP certificate attached.<br>CoPP or free sale certificate not attached as product not approved yet. |
| 14 | Pre-clinical/clinical safety studies | Attached in investigator Brochure. |
| 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. | Number of patients enrolled at each site in Pakistan: |

| | | |
|---|---|---|
| | | i. Shifa International Hospital, Islamabad. (200 Subjects for Phase-II & 2225 Subjects for Phase-III)<br>ii. Al-Shifa Trust Research Center, Rawalpindi. (2225 Subjects for Phase-III)<br>iii. Central Park Teaching Hospital, Lahore. (2225 Subjects for Phase-III)<br>iv. Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad. (2225 Subjects for Phase-III)<br>v. Indus Hospital and Health Network, Karachi. (2225 Subjects for Phase-III)<br>vi. Central Hospital, Gujranwala. (2225 Subjects for Phase-III)<br>vii. Avicenna Hospital & Medical College Lahore. (2225 Subjects for Phase-III)<br>viii. National Hospital and Medical Centre, Lahore. (2225 Subjects for Phase-III)<br>Total 200 Subjects for Phase-II at Shifa International Hospital & 2225 Subjects for Phase-III on each site in Pakistan only. |
| 19 | Name of Monitors & Clinical Research Associate | M/s DRK Pharma Solutions Pakistan (Pvt) Ltd., Karachi.<br>1. Talha Javed, Clinical Project Manager<br>2. Ashfaq Ahmed, CRA, Shifa International Hospital, Islamabad.<br>3. Fahd Ali Awan, CRA- Al-Shifa Trust Research Center, Rawalpindi.<br>4. Abida Hashmi, CRA- Central Park Teaching Hospital, Lahore<br>5. Ali Faizan, CRA- Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad.<br>6. Shiza Ashraf, CRA- lndus Hospital and Health Network, Karachi<br>7. Sana Rafique, CRA- Central Hospital, Gujranwala<br>8. Salman Pervaiz, CRA- Avicenna Hospital & Medical College Lahore<br>9. Humayun Aslam, CRA- National Hospital and Medical Centre, Lahore |
| 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. | Attached. |
| 22 | Duration of trial | The duration of participation of each individual subject is approximately 12 months from the consent to last visit. Estimated timelines for study startup, recruitment and close out activities are 9 months.<br>Total duration of the trial is **21** months. |
| 23 | Undertaking on Stamp paper | Attached. |

As per the application trial will be conducted only in Pakistan. Application is for Phase II/III clinical trial. The phase II & III trial will be conducted at Shifa International Hospital and on other sites only phase III trial will be conducted. As per security of file, the requisite documents and fee is attached with the application.

**Decision: -**

*The CSC after detailed discussion and deliberation decided as follows:*

a. *to approve the subject study for phase-II only to be conducted at **Shifa International Hospitals Ltd, Islamabad**. The applicant will submit safety, efficacy, immunogenicity and phase-II clinical study data along with judgment of Data Safety Monitoring Board (DSMB) to the Division of Pharmacy Services DRAP. The CSC after considering efficacy and acceptable safety profile and DSMB report, will further consider and decide the Phase-III trial of instant study.*
b. *to approve 18900 doses of IMPs (LYB001 +Placebo) for import after getting necessary approval/ NOC from concerned DRAP field office.*

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**AGENDA ITEM IV:**

**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 Accelrated 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:

vii. **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 metres, 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<br>Protocol No. HIP ATTACKL-2<br>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.<br>Canada, USA, Mexico, Belgium, Denmark, Finland, Italy, Neitherland, Poland, Spain, United Kingdom, South Africa, Saudi Arabia, Chilli, Australia, Kong Kong, India, Nepal, Malysia, 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**<br>**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 | 10. Dr Tehreem Zahid<br>11. Dr. Sundus Dadan<br>12. Dr Palwsha Alvi<br>13. Raja Waseem Akram<br>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.*

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**AGENDA ITEM V:**

**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 Cowk, 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:

viii. **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 | Starpharma Pty Limited, 4-6 South Ampton Crescent |

| | | |
|---|---|---|
| | Abbotsford, Victoria 3067, Australia. | 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.<br>One actuation deliverls volume of 100µl.<br>Approximate daily delivered volume 900µl. | One spray actuation 4 time a day in each Nostril.<br>One actuation deliverls volume of 100µl.<br>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 | Pulmonologst | **Post Market Cofirmatory.** | **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.<br><br>**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 Tehareen. |
| 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.*

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**AGENDA ITEM VI:**

**APPLICATION FOR APPROVAL AND REGISTRATION OF CLINICAL TRIAL TITLED "A RANZOMIZED, BLINDED, PARALLEL CONTROLLED PHASE III STUDY TO EVALUATE THE IMMUNOGENICITY AND SAFETY OF SARS CoV-2 mRNA VACCINE (LRVNA009) AS HETEROLOGOUS BOOSTER IN PARTICIPANTS AGED 18 YEARS AND OLDER VACCINATED 2 DOSES INACTIVATED SARS-CoV-2 VACCINE" (F. No.03-07/2022-DD (PS).**

The Case is from Muhammad Khurram Zaki Khan, CEO Dimension Research CRO & SMO, Karachi, wherein he has requested for registration and approval of subject mention trial/ study.

2. Application is on prescribed Form-II from M/s Dimension research CRO, along with Prescribed fee of Rs.200000/-, deposited vide slip number 0377603156, dated 24th July 2022.

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

| S. No. | Document | Remarks |
|---|---|---|

| | | |
|---|---|---|
| 1 | Application on prescribed Form-II | Attached.<br>**Form-II not signed.** |
| 2 | Fee | Prescribed fee of Rs.200000/-, deposited vide slip number 0377603156, dated 24th July 2022 |
| 3 | Investigator Brochure (s) | Attached |
| 4 | Final protocol | Attached.<br>**Not signed by PI and sponsor** |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached |
| 6 | List of participating countries | 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. | SARS-CoV-2 mRNA Vaccine (LVRNA009) 550 +138 boxes.<br>Inactivated SARS-CoV-2 (Vero Cell) (CoronaVac) 550+50 boxes.<br>**Justification required for 138, 50 extra Boxes.** |
| 9 | Site of the trial | National Institute of Health, Islamabad. |
| 10 | Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members. | IRB approval attached.<br>**Mrs. Ghazala Parveen is Sub-Investigator and also member of IRB.** |
| 11 | Approval of National Bio-ethics Committee (NBC) | NBC approval reference No.4-87/NBC-798/22/2331, dated 17th June 2022 (a New approval required) |
| 12 | CV's of the Investigators | CVs of Major General Prof. Dr. Aamer Ikram, Mrs. Ghazala Parveen and Dr. Omera Naseer are attached. |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | GMP certificate of M/s Ningbo Rongan Bio-Pharmaceutical co., Ltd is attached **with scope of Inspection "Preventive Biological Products [Rabies Vaccine (Vero Cell) for Human Use, Freeze dried]"**<br>**GMP Certificate with IMPs manufacturing or IND approval is required.**<br>**GMP Certificate, CoPP for CoronaVac is required.** |
| 14 | Pre-clinical/clinical safety studies | Attached. |
| 15 | Summary of Protocol | Provided in protocol. |

| | | |
|---|---|---|
| 16 | Summary of Investigator Brochure | **Not attached.** |
| 17 | Adverse Event Reporting Form | **Applicant has attached Unique Case Reporting Form instead of Adverse Event Reporting Form** |
| 18 | No of patients to be enrolled in each center. | 1,100 subjects. |
| 19 | Name of Monitors & Clinical Research Associate | Mrs. Sadaf Khuram<br>Miss Maleeha Arshad<br>Miss Wajeeha Nuzhat<br>Of M/s Dimension Research CRO |
| 20 | Evidence of registration in country of origin. | Drug Under Phase III Trial<br>**Evidence in country of origin for CoronaVac is required.** |
| 21 | Copy of registration letter (if registered in Pakistan) | **Registration letter for CoronaVac is required.** |
| 22 | Sample of label of the investigational product / drug. | Attached. |
| 22 | Duration of trial | From start of enrolment till data lock will be approximately 20 months. |
| 23 | Undertaking on stamp paper | Attached. |

4. In the view of above following are the observations;

i. Form-II is from CEO of a CRO instead of responsible party i.e. PI or Sponsor.
ii. Form-II not signed.
iii. Justification required for 138, 50 extra Boxes to be imported/ purchased.
iv. Mrs. Ghazala Parveen is Sub-Investigator and also member of IRB that is conflict of interest.
v. GMP certificate of M/s Ningbo Rongan Bio-Pharmaceutical co., Ltd is attached with scope of Inspection "Preventive Biological Products [Rabies Vaccine (Vero Cell) for Human Use, Freeze dried]" GMP Certificate with IMPs manufacturing or IND approval is required.
vi. GMP Certificate, CoPP for CoronaVac is required.
vii. Investigator Brochure not attached.
viii. Evidence in country of origin for CoronaVac is required.
ix. Registration letter for CoronaVac is required.
x. The published data for Phase-I & II along with study protocol for Phase-I & II are required.
xi. NIH is not approved as CTS for generalized clinical trials.
xii. Agreement and details/ procedure for sample transfer not attached.

5. **The shortcomings were communicated vide this office letter No.F.03-07/2022 DD (PS) dated 3rd October 2022 and reply is still awaited.**

6. The case was placed before CSC in its 35th meeting held on 13th October 2022 and was decided as follows;

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

i. *Form-II is from CEO of a CRO instead of responsible party i.e. PI or Sponsor.*
ii. *Form-II not signed.*
iii. *Justification required for 138, 50 extra Boxes to be imported/ purchased.*
iv. *Mrs. Ghazala Parveen is Sub-Investigator and also member of IRB that is conflict of interest.*
v. *GMP certificate of M/s Ningbo Rongan Bio-Pharmaceutical co., Ltd is attached with scope of Inspection "Preventive Biological Products [Rabies Vaccine (Vero Cell) for Human Use, Freeze dried]" GMP Certificate with IMPs manufacturing or IND approval is required.*
vi. *GMP Certificate, CoPP for CoronaVac is required.*
vii. *Investigator Brochure not attached.*
viii. *Evidence in country of origin for CoronaVac is required.*
ix. *Registration letter for CoronaVac is required.*
x. *The published data for Phase-I & II along with study protocol for Phase-I & II are required.*
xi. *NIH is not approved as CTS for generalized clinical trials.*
xii. *Agreement and details/ procedure for sample transfer not attached.*

The shortcomings were communicated vide this office letter 03-07/2022 dated 3rd October 2022 and case was also placed before CSC in its 35th meeting held on 13th October 2022 and case was deferred for fulfilment of above mentioned shortcomings.

The applicant has submitted the response to above mentioned letters dated 11.10.2022, 18.10.2022, 29.11.2022 and 10.01.2023. The series of replies of the applicant has been evaluated in tabulated form as follows;

| **Queries/ Shortcoming** | **Reply** |
|---|---|
| Form-II is from CEO of a CRO instead of responsible party i.e. PI or Sponsor. | Signed Form II by Major General Aamir Ikram is attached. |
| Form-II not signed. | Signed Form II by Major General Aamir Ikram is attached. |
| Justification required for 138, 50 extra Boxes to be imported/ purchased. | The extra boxes will be imported to take care of the number of drop out volunteers. |
| Mrs. Ghazala Parveen is Sub-Investigator and also member of IRB that is conflict of interest. | Attendance sheet of IRB meeting is attached.<br>**The members in attendance sheet are not as per IRB notification.** |
| GMP certificate of M/s Ningbo Rongan Bio-Pharmaceutical co., Ltd is attached with scope of Inspection "Preventive Biological Products [Rabies Vaccine (Vero Cell) for Human Use, Freeze dried]" GMP Certificate with IMPs manufacturing or IND approval is required. | GMP certificate attached.<br><br>**Drug Clinical Trial Approval attached.** |
| GMP Certificate, CoPP for CoronaVac is required. | EUA for CoronaVac is attached.<br>**GMP certificate, CoPP of CoronaVac not attached. The CoronaVac EUA has been issued "for EPI/ Government supply (Not for sale in market)".** |
| Investigator Brochure not attached. | Investigator Brochure attached. |
| Evidence in country of origin for CoronaVac is required. | EUA from Pakistan attached. |
| Registration letter for CoronaVac is required. | EUA attached. |
| The published data for phase I & II along with study protocol for phase-I & II are required. | Data has not been published yet. |

| | |
|---|---|
| NIH is not approved as CTS for generalized clinical trials. | Approved CTS for Phase III & IV clinical Trials (For vaccines only) |
| Agreement and details/ procedure for sample transfer not attached. | Attached. |

As per Notification dated 26th November 2021 following are IRB members of NIH;

| | |
|---|---|
| Dr. Muhammad Salman | Mrs Ghazala Perveen |
| Dr. Jamil Ansari | **Mr. Tanveer Ibrahim** |
| Dr. Najma Javed | Hafiz Muhammad Sana Ullah |

But following members participated and approved the study;

| | |
|---|---|
| Dr. Muhammad Salman | **Dr. Rahim Shah** |
| Dr. Najma Javed | Dr. Jamil Ansari |
| Hafiz Muhammad Sana Ullah | |

Further, the applicant has submitted Form-II signed by Maj. Gen.Aamer Ikram wherein he has also mentioned M/s Agha Khan University Hospital (AKUH) Karachi as CTS.

The applicant intends to conduct phase-III clinical trial using CoronaVac as comparator vaccine. The CoronaVac is registered in Pakistan with remarks **for EPI/ Government supply (Not for sale in market).** As per EUA it is not clear that CoronaVac has registration as booster dose. Further the blinding procedure of the IMPs needs to be clarified.

**Discussion: -**

*The CSC gave opportunity to the applicant and National Investigator Pakistan to brief the members about the case. Mr. Xia Wei and Miss Chen Xin Hui attend the meeting physically while Mr. Mike Li with his team (from Stem) and Miss Luo Liping (from AIM) joined through Zoom link. PI didn't join the meeting. The committee members asked different queries from the people joined on behalf of sponsor. They replied in Chinese language and were translated by Mr. Xia Wei and Miss Chen Xin Hui in English to brief committee members. Queries of CSC and their response is as follows:*

a. *Reason for not performing reproductive toxicity, genotoxicity and carcinogenicity. Sponsor representative replied that, usually the studies are long term studies and are under process and hopefully will be completed till end of April 2023. Required safety and efficacy studies have been performed in Phase-I trial.*
b. *Reason for selection of instant dose as booster dose. It was replied that phase I studies were carried with 25µg, 50 µg, 100µg and placebo while phase II studies were performed with 50µg and 100µg doses. The representative replied that sponsor has selected 100µg dose primary vaccine trial of phase III in other countries while 50µg has been selected as booster dose in phase III trial. He further explained that as per their view 50µg is safer than 100 ug. Such other queries were also asked by the CSC members that were replied by the sponsor.*

**Decision: -**

*The CSC after detailed discussion and deliberation decided as follows:*

a. *to approve the clinical study titled as **"A RANZOMIZED, BLINDED, PARALLEL CONTROLLED PHASE III STUDY TO EVALUATE THE IMMUNOGENICITY AND SAFETY OF SARS CoV-2 mRNA VACCINE (LRVNA009) AS HETEROLOGOUS BOOSTER IN PARTICIPANTS AGED 18 YEARS AND OLDER VACCINATED 2 DOSES INACTIVATED SARS-CoV-2 VACCINE",*** to be conducted at following site(s)

i. *National Institute of Health (NIH), Islamabad.*
ii. *Aga Khan University Hospital, Karachi.*

b. *To approve import 688 (550+138 extra) doses of LRVNA009 after getting necessary approval from concerned DRAP office.*
c. *Comparator vaccine can be used after getting permission / NOC form Extended Program for Immunization (EPI).*

**AGENDA ITEM VII:**

**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. (F. NO.03-24/2023 DD (PS).**

The case is an application from Dr. Saud Ghazi, CNIC No.37405-0341695-5, Consultant Medical Oncologist, Shifa International Hospital Limited, Sector H-8/4, Islamabad, dated 23rd December, 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 Slip number. 15673480871, dated 19th December, 2022.

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

iv. **Sponsor:** JSC BIOCAD, 198515, Saint Peter Sburg, the Settlement of Strelna, UL. Svyazi, D. 34, Lit. A.

**Brief Summary:** The clinical study is designed as a randomized, double-blind trial. Subjects with unresectable, metastatic melanoma, or recurrent skin melanoma will be randomized to one of the two study groups (BC-201 group and Keytruda group) at a 1:1 ratio. The subjects will receive a double-blind treatment with BCD-201 or Keytruda administered intravenously at a dose of 200 mg once every 3 weeks for 24 weeks or until disease progression or unacceptable toxicity. After completion of double-blind treatment with BCD-201/Keytruda, subjects are rolled over to open label extension period of the study and will receive BCD-201 therapy as a part of this protocol. Subjects will relieve study therapy for a total treatment duration of 105 weeks from randomization or until disease progression or signs of unacceptable toxicity.

**v. Study Vaccine/IMPs required along with justification:**

| **Intervention name** | **BCD 201** | **Keytruda** |
|---|---|---|
| **Sourcing** | JSC BIOCAD, Russia | JSC BIOCAD, Russia (Merck) |
| **Specification** | 100mg/ 4ml Vial | 100mg/ 4ml Vial |
| **Main ingredients** | Pembrolizumab | Pembrolizumab |
| **Formulation** | Injection to be diluted in N/Saline | Injection to be diluted in N/saline |
| **Appearance** | Clear to slightly opalescent, colorless to light yellow liquid. | Clear or slightly opalescent from colorless to light brown liquid. |
| **Dose regimen and route of administration** | 200mg diluted in 100 ml Normal saline administered Intravenous | 200mg diluted in 100 ml Normal saline administered Intravenous |
| **Storage** | 2-8oC away from light, avoiding freezing | 2-8oC away from light, avoiding freezing |
| **Batch number and expiration date** | To be determined | To be determined |

**vi. Quantity of IMPs required along with justification:**

| **Study Intervention** | **Test Drug** | **Comparator** |
|---|---|---|
| **Intervention Name** | BCD 201 | Keytruda |

| | | |
|---|---|---|
| **Dose Formulation** | Injection | Injection |
| **Each Vial Contain** | 100mg/ 4ml Vial | 100mg/ 4ml Vial |
| **Quantity to be imported** | 2940 vials | 840 vial |
| **Total box to be imported** | ---- | ----- |
| **Total subjects to be recruited in Pakistan** | 50 | |

**vii. Source of Investigational Medical Products (IMPs):**

- JSC BIOCAD Russia.

**viii. Number of subjects to be recruited:** **50** Subjects

**ix. Anticipated cost of the project:** USD 15,00,000/-

**x. Study design & details:**

| | |
|---|---|
| | Interventional (Clinical Trial) |
| Estimated Enrollment : | 523 participants (Globally) |
| Allocation: | Randomized |
| Intervention Model: | Parallel Treatment |
| Masking: | Double (Participant, Investigator) |
| Primary Purpose: | Treatment of Melanoma |
| Official Title: | 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. |

3. 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. Saud Ghazi (National-PI) | Oncologist | Phase- III | --- |
| **Shaheed Zulfiqar Ali Medical University, Islamabad.** | Dr.Qasim M Buttar, Site-PI | Oncologist | Phase-III | --- |
| **Shaukat Khanam memorial Cancer Hospital & Research Center, Lahore.** | Dr. Samir Fasih, Site PI | Oncologist | Phase-III | |
| **Allama Iqbal Medical College/ Jinnah Hospital, Lahore.** | Dr Kausar bano, Site-PI | Oncologist | Phase-III | **Site not approved** |
| **King Edward Medical university/ Myo Hospital, Lahore.** | Dr. Abbas Khakhar, Site-PI | Oncologist | Phase-III | **Site not approved** |
| **Nishtar Medical University & Hospital Multan** | Prof. Dr.Ahmed Ijaz masood, Site-PI | Oncologist | Phase-III | **Site not approved/ Withdrwan** |
| **Allied Hospital Faisalabad.** | Dr. Muhammad Tahir Bashir | Oncologist | Phase-III | **Site not approved.** |

Primary & Secondary Objectives

i. To compare the overall response rate (ORR) in the BCD-201 group and the Keytruda Group.(Primary)
ii. To compare the secondary efficacy end points in the BCD-201 group and the Keytruda Group.
iii. To compare the safety profiles of the BCD-201 group and the Keytruda Group.
iv. To compare the pharmakokinets BCD-201 and Keytruda.
v. To compare the immunogenicity BCD-201 and Keytruda.
vi. To assess the long term safety parameters following intravenous administration of BCD-201.
vii. To assess the efficacy of BCD-201 in subjects based on overall and progression-free survival.
viii. To assess the long term immunogenity of BCD-201 based on the incidence of binding and neutralizing antibodies of Pembrolizumab.

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. 15673480871, dated 19th December, 2022. |
| 3 | Investigator Brochure (s) | Russian language<br>English Language |
| 4 | Final protocol | Protocol number; BCD-201-2 Version 2.0 of July 14, 2022 is Attached |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached. |
| 6 | List of participating countries | Russia, Belarus, India, 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. | BCD 201 Keytruda<br>2940 Vials 840 vials |
| 9 | Sites of the trial | 1.Shifa International Hospitals Ltd, Islamabad<br>2.Shaheed Zulfiqar Ali Medical University, Islamabad.<br>3.Shaukat Khanam Memorial Cancer Hospital & Research Center, Lahore.<br>4.Allama Iqbal Medical College/ Jinnah Hospital, Lahore.<br>5.King Edward Medical university/ 5.Mayo Hospital, Lahore.<br>6.Nishtar Medical University & Hospital Multan (**Site withdrawn**).<br>7.Allied Hospital Faisalabad. |
| 10 | Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members. | IRB approval of M/s SKMCH&RC and Nishtar Medical University and Hospital not attached. |
| 11 | Approval of National Bio-ethics Committee (NBC) | Approved vide reference number 4-87/NBC-890/22/811 dated 15th December 2022. |
| 12 | CV's of the Investigators | CVs of following (PI & Co-PI) experts are attached.<br>ix. Dr. Saud ghazi (National-PI) Shifa International Hospital, Islamabad<br>x. Dr. Qasim M Buttar, Site-PI, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad.<br>xi. Dr. Sameer Fasih, Site-PI, Shaukat Khanam Memorial Hospital & Cancer Research Center, Lahore.<br>xii. Dr. Kausar Bano, Site-PI, Jinaah Hospital Lahore.<br>xiii. Dr. Abbas Khkhar, Site-PI, Myo Hospital, Lahore.<br>xiv. Prof. Dr. Ahmed ijaz Masood, Site-PI, Nishtar Hospital, Multan. |

| | | |
|---|---|---|
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | GMP certificate JSC BIOCAD attached.<br>attached.<br>GMP certificates of Merck, Neitherland and Organon Heist B.V. Belgium attached.<br>Ketruda is registered with EMA |
| 14 | Pre-clinical/clinical safety studies | Attached in investigator Brochure. |
| 15 | Summary of Protocol | Attached |
| 16 | Summary of Investigator Brochure | Attached. |
| 17 | Adverse Event Reporting Form | SAE Form, Over Dose Report Form, Death Report Form, Pregnancy Report Form attached. |
| 18 | No of patients to be enrolled in each center. | Competitive recruitment. |
| 19 | Name of Monitors & Clinical Research Associate | M/s DRK Pharma Solutions Pakistan (Pvt) Ltd., Karachi.<br>1. Syed Rooh Ul Arifeen, Clinical Project Manager<br>2. Mobeen Amjad, Unblided CRA,<br>3. Attiqa Kiani, CRA, Shifa International Hospital, Islamabad.<br>4. Shinza Shahid, CRA- SZABM university, Islamabad..<br>5. Sana Rafique, CRA- SKMCH&RC, Lahore.<br>6. Muhammad Umar Yaseen,, CRA- Jinnah Hospital, Lahore.<br>7. Muhammad faith Mobeen Hashmi,, CRA- Myo Hospital, Lahore.<br>8. Talha Shafiq, CRA- Nishtar Hospital, multan |
| 20 | Evidence of registration in country of origin. | **Product not registered yet.**<br>**Registered EMA.** |
| 21 | Copy of registration letter (if registered in Pakistan) | **Not provided.** |
| 22 | Sample of label of the investigational product / drug. | Attached. |
| 22 | Duration of trial | 33 weeks |
| 23 | Undertaking on Stamp paper | Attached. |

5. Another request was submitted by Dr. Syed Rooh Ul Arifeen, Project Manager wherein he has submitted that M/s Nishtar Medical University & Hospital Multan has been excluded from the trial whereas Allied Hospital, Faisalabad has been included in this trial. The applicant has attached approval letters of Central Drugs Standard Control Organization, Government of India and Ministry of Health of the Russian Federation subject mentioned study for phase III trial.

6. The BCD 201 contains Pembrolizumab 100mg/4ml is being compared with Keytruda in phase III trial after phase I trial. The trial is competitive recruitment trial. The comparator product Keytruda is registered with US-FDA, Health Canada, TGA and EMA.

7. In the light of above, it is proposed that case may be placed before CSC in forthcoming meeting and meanwhile the protocol and Investigator brochure may be shared with the CSC members for review.

The case is submitted for consideration of CSC.

**Decision: -**

*The CSC after detailed discussion and deliberation decided as follows:*

a. *to approve the 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"** for phase-III to be conducted at following sites:*
   i. Shifa International Hospitals Ltd, Islamabad
   ii. Shaheed Zulfiqar Ali Medical University, Islamabad.
b. *to approve import of 840 blinded vial (BCD201/ Keytruda) and 2940 vials of BCD201. The applicant may import the Investigation Medicinal Products (IMPs) in part shipments after getting necessary approval/ NOC from concerned DRAP office.*

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**AGENDA ITEM VIII:**

**DECREASING POSTOPERATIVE BLOOD LOSS BY TOPICAL VS INTRAVENOUS TRANEXAMIC ACID IN OPEN CARDIAC SURGERY (DEPOSITION) TRIAL. (F. NO.03-21/2022 DD (PS).**

The case is an application from Dr. Muhammad Asghar Nawaz, CNIC No.35200-9121235-9, Consultant Cardiothoracic Surgeon, Shifa International Hospital Limited, Sector H-8/4, Islamabad, wherein request has been made for approval of Clinical Trial titled "Decreasing Postoperative blood loss by topical vs intravenous Tranexamic Acid in open Cardiac Surgery (Deposition) Trial". Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide Slip number. 68926635769, dated 6th October, 2022. The trial is registered with US Trial Registry https://clinicaltrials.gov/ct2/show/NCT03954314 with identifier NCT03954314.

2 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, C-1-236 Hamilton, Ontario, Canada L8L 2X2

**Brief Summary:** DEPOSITION is a multi-centre, double-dummy, randomized controlled trial comparing topical with intravenous administration of tranexamic acid in patients undergoing on-pump cardiac surgery. Subjects will be randomized in a 1:1 ratio to topical TxA (IV placebo + topical TxA) or intravenous TxA (IV TxA + topical placebo). The aim of the trial is to show that topical TxA is *superior* to the usual intravenous TxA approach (i.e. a superiority trial). A schematic diagram of the trial design, including treatment groups and the primary outcome is provided.

The aim is to conduct a double-dummy multi-centre randomized controlled clinical trial of application of topical dose of Tranexamic acid (TxA) versus the usual intravenous TxA in patients undergoing on-pump cardiac surgery.

Detailed Description:

Postoperative bleeding related to open cardiac surgery increases the rates of complications and mortality. It results from the blood thinners that are needed for use. Intravenous tranexamic acid (TxA) has become a mainstay in cardiac surgical procedures for decreasing bleeding and minimizing transfusion requirements. Although intravenous TxA is usually well tolerated, there is a well-known risk (1 to 4%) of postoperative seizures. This is due to the similarity between TxA and the brain tissues. The aim is to eliminate the risk of seizures but to maintain the protection against bleeding. When TxA is used directly on the tissues (topically) for other type of surgeries (joints), TxA is effective to reduce blood loss and transfusions. The aim is to prove that direct application of TxA on the heart can eliminate postoperative seizures and reduce the amount of blood transfusions in patients who have cardiac surgery.

**ii. Study Vaccine/IMPs required along with justification:**

| **Intervention name** | **Tranexamic Acid (IV) vs Placebo (Topical)** | **Tranexamic Acid (Topical) vs Placebo (IV)** |
|---|---|---|
| **Sourcing** | Hilton Pharma, Pakistan | Hilton Pharma, Pakistan |
| **Specification** | 500mg/ 5ml Injection | 500mg/ 5ml Injection |

| | | |
|---|---|---|
| **Main ingredients** | Tranexamic Acid vs Placebo | Tranexamic Acid vs Placebo |
| **Formulation** | Injection | Injection |
| **Appearance** | Clear liquid. | Clear liquid. |
| **Dose regimen and route of administration** | 1gm-10gm of Tranexamic Acid Placebo (Saline) | 5gm-10gm of Tranexamic Acid Placebo (Saline) |
| **Storage** | 1gm-10gm of Tranexamic Acid Placebo (Saline) | 1gm-10gm of Tranexamic Acid Placebo (Saline) |
| **Batch number and expiration date** | To be determined | To be determined |

**iii. Quantity of IMPs required along with justification:**

Will be purchased 1000 ampoule locally from Shifa Pharmacy, Islamabad.

**iv. Source of Investigational Medical Products (IMPs):**

- Hilton Pharma, Karachi, Pakistan.

**v. Number of subjects to be recruited:** 1-2/week total 50 Subjects in Pakistan

**vi. Anticipated cost of the project:** USD 260/ subject/-

**vii. Study design & details:**

| | |
|---|---|
| Study Type | Interventional (Clinical Trial) |
| Estimated Enrollment : | 3800 participants (Globally) |
| Allocation: | Randomized |
| Intervention Model: | Parallel Assignments |
| Masking: | Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |
| Primary Purpose: | Prevention |
| Official Title: | Decreasing Postoperative Blood Loss by Topical vs. Intravenous Tranexamic Acid in Open Cardiac Surgery (DEPOSITION) Study |

3. 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. Muhammad Asghar Nawaz | Consultant Cardiothoracic Surgeon | Phase- III | --- |
| **Rehman Medical Institute, Peshawer.** | **Not mentioned** | **Not Mentioned** | | |

Primary & Secondary Objectives

i. To determine in patients undergoing on pump cardiac surgery if topical TxA (Intr-pericardial) is superior to the usual intravenous TxA administration for reducing risk of in hospital red blood cell transfusion or seizure (**Primary**).

ii. To determine whether topical TxA (Intra Pericardial) compared with intravenous TxA administration reduces the risk of in hospital red blood cell transfusion.

iii. To determine whether topical TxA (Intra Pericardial) compared with intravenous TxA administration reduces the risk of in hospital seizure.

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. 68926635769, dated 6th October, 2022. |
| 3 | Investigator Brochure (s) | Attached. |
| 4 | Final protocol | Protocol number; BCD-201-2 Version 2.0 of July 14, 2022 is Attached |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached. |

| | | |
|---|---|---|
| 6 | List of participating countries | Canada, Czech Republic, Malysia, Poland, Russia, India, 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. | **Will be purchased locally from Shifa Pharmacy** |
| 9 | Sites of the trial | 1.Shifa International Hospitals Ltd, Islamabad<br>2. Rehman Medical Institute, Peshawer, Pakistan. |
| 10 | Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members. | **IRB approval, IRB Notification of M/s Rehman Medical Institute not attached.** |
| 11 | Approval of National Bio-ethics Committee (NBC) | Approved vide reference number 4-87/NBC-890/22/88 dated 28th July 2022. |
| 12 | CV's of the Investigators | CV of Dr. Muhammad Asghar Nawaz attached.<br>**CV of PI at Rehman Medical Institute not attached.**<br>of 85-following (PI & Co-PI) experts are attached. |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | GMP certificate of M/s Hilton Pharma, Karachi and COA of Lot No. TSHTA16401 attached.<br>**Details regarding Saline manufacturer not attached.** |
| 14 | Pre-clinical/clinical safety studies | Attached.<br>**Phase I & II data required.** |
| 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. | 50 patients to be enrolled in Pakistan. |
| 19 | Name of Monitors & Clinical Research Associate | 14. Dr Tehreem Zahid<br>15. Dr. Sundus Dadan<br>16. Raja Waseem Akram<br>All are employees of Shifa International Hospital, Islamabad. |
| 20 | Evidence of registration in country of origin. | **NOC of Deposition Trial attached.** |
| 21 | Copy of registration letter (if registered in Pakistan) | Attached. |
| 22 | Sample of label of the investigational product / drug. | Not attached. |
| 22 | Duration of trial | 36 month (3 Years) |
| 23 | Undertaking on Stamp paper | Attached. |

5. In this case the Tranexamic Acid Injection of Hilton Pharma, Karachi will be used through Intravenous route and same will be applied topically on cardiac muscles during on pump cardiac surgery. For topical use TxA will be poured into the pericardial and mediastinal cavities after protamine administration. Blinding procedure of TxA and placebo not clearly mentioned. Details of manufacturer of saline to be used as placebo not provided. CV of PI at Rehman Medical Institute along with IRB approval is required. Phase I/ II data of the subject trial is required.

6. In the light of above, it is proposed that Cardiac Surgeon may be coopted for the case in forthcoming CSC meeting.

**Decision: -**

*The CSC after detailed discussion and deliberation decided to defer the case for expert opinion from person having vast experience in cardiac surgery. The expert person will be nominated the Chairman and will be taken as co-opted member for CSC meeting to brief the case. The CSC further decided that meanwhile, applicant will submit reply to the following shortcomings/ queries.*

*i. Details of manufacturer of saline to be used as placebo is required.*
*ii. GMP and CoPP/ Free Sale Certificate of Saline manufacturer required.*
*iii. Procedure for blinding of IMPs required.*
*iv. CV of PI at Rehman Medical Institute along with IRB approval is required.*
*v. Phase I/II data of the trial is required.*
*vi. The approval of clinical trial in other countries, if any, is required.*

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**AGENDA ITEM IX:**

**A MULTICENTER. DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED PHASE II/III STUDY TO EVALUATE THE EFFICAY, SAFETY AND PHARMAKOKINETICS OF JT001 (VV116) FOR THE EARLY TRAETMENT OF CRONAVIRUS DISEASE 2019 (COVID-19) IN PARTICIPANTS WITH MILD TO MODERATE COVID-19. (F. No.03-28/2023-DD (PS)**

The case is an application from Prof. Dr. Ume Sughra, CNIC No.37405-0579220-0, Director Research, Al-Shifa Trust Eye Hospital, Jehlam road, Rawalpindi, 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. 05722831, dated 13th December, 2022.

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

i. **Sponsor:** Shanghai JunTop Biosciences Co., LTD & Vigonvita Life sciences Co., Ltd.

**Brief Summary:** This study aims to evaluate the efficacy, safety and pharmacokinetics of JT001 (VV116) for the early Treatment of Coronavirus Disease 2019 (COVID-19) in participants with mild to moderate COVID-19, at high risk for progression to severe COVID-19, including death.

Current treatment for COVID-19 is still limited despite rapidly evolving and local treatment guidelines continue to be updated with emerging data. As of Jun 28, 2022, four neutralizing monoclonal antibodies (bebtelovimab, sotrovimab, bamlanivmab + etesevimab, casirivimab + imdevimab) and two oral SARS-CoV-2 antiviral agents (Molnupiravir and nirmatrelvir/ritonavir tablets [Paxlovid]) have received Emergency Use Authorization (EUA) from FDA, for the treatment of non-hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19 and more drugs are under development. worldwide. However, the virus SARS-CoV-2 changes overtime, such as Alpha, Beta, Delta, and the emerging Omicron variant. It is reported that neutralizing monoclonal antibodies may lose their efficacy against certain variants. Remdesivir is an antiviral agent administered intravenously and is conditionally approved by FDA for the treatment of hospitalized or non- hospitalized patients diagnosed with mild-to-moderate COVID-19 who are at high risk for progression to severe COVID-19 In China, a neutralizing monoclonal

antibodies treatment has been approved, and Paxlovid has been conditionally approved by NMPA on Feb 11 2022. However, there remains a need for more orally bioavailable and effective antiviral agents for treatment of COVID-19.

There is an increased risk for progression to severe disease with increasing age and/or presence of underlying medical conditions in adults. With increasing numbers of cases and deaths worldwide, and very limited treatment options, there is still an immediate unmet medical need for new effective therapies. JT001 (VV116) is a novel drug candidate with demonstrated activity against SARS-CoV-2 in vitro, efficacy against coronaviruses in animal models, and a high barrier to viral resistance. To date, JT001 (VVI16) has shown good safety and tolerability in completed clinical studies, including three Phase I, one Phase II and one Phase III clinical studies. In the Phase III study, time to sustained clinical recovery and time to sustained clinical symptom resolution after JT001 (VV116) treatment were not inferior to the positive control drug Paxlovid in mild to moderate COVID-19 patients with high risk of progression to severe disease and death.

**ii. Study IMPs required along with justification:**

| **Intervention name** | **JT001 (VV116)** | **Placebo** |
|---|---|---|
| **Sourcing** | Shangai Desano Bio-Pharmaceuticals, Co., Ltd | Shangai Desano Bio-Pharmaceuticals, Co., Ltd |
| **Specification** | 100mg/ Tablet | 0 mg/Tablet |
| **Main ingredients** | Deuremidevir Hydrobromide | Deuremidevir Hydrobromide |
| **Formulation** | Tablet | Tablet |
| **Appearance** | Film coated Tablet. | Film coated Tablet. |
| **Dose regimen and route of administration** | First Day: 600mg Q12 H x 2 times<br>2-5 Days; 300mg Q12 H x 8 times | First Day: 6 Tabs Q12 H x 2 times<br>2-5 Days; 3 Tabs Q12 H x 8 times |
| **Storage** | Room Temperature (10-30°C) | Room temperature (10-30 °C) |
| **Batch number and expiration date** | To be determined | To be determined |

**iii. Quantity of IMPs required along with justification:**

| **Study Intervention** | **Test Drug** | **Placebo** |
|---|---|---|
| **Intervention Name** | JT001 (VV116) | Placebo |
| **Dose Formulation** | Tablets | Tablets |
| **Each Bottle Contains** | 20 tablets/ Bottle | 20 tablets/ Bottle |
| **Quantity to be imported** | Total 9984 Tablets (192 subjects + 30% Wastage) | |
| **Total box to be imported** | 250 Carton (2 Bottles/ Carton) | |
| **Total subjects to be recruited in Pakistan** | 192 | |

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

**iv. Number of subjects to be recruited:** 192 Subjects (Pakistan)

**v. Anticipated cost of the project:** USD 7,61,889/-

**vi. Study design & details:**

| | |
|---|---|
| Study Type | Interventional (Clinical Trial) |
| Estimated Enrollment : | 1310 participants (Globally) |
| Allocation: | Randomized |
| Intervention Model: | Parallel Assignments |
| Masking: | Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) |
| Primary Purpose: | Treatment |

| | |
|---|---|
| Official Title: | A Multicenter, Double-blind, Randomized, Placebo-Controlled, Phase II/III Study to Evaluate the Efficacy, Safety and Pharmacokinetics of **JT001** (**VV116**) for the Early Treatment of Coronavirus Disease 2019 (COVID-19) in Participants With Mild to Moderate COVID-19. |

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. Syed Faisal Mehmood (Site-PI) | Infectious Diseases | Phase- III | --- |
| **Rehman medical Institute, Peshawer.** | Dr. Sajjad Ali, Site-PI | Medicine and Infectious Diseases | Phase-III | --- |
| **Maroof International Hospital, Islamabad.** | Dr.Sajjad Naseer, Site PI | Pulmonologist | Phase-III | ------ |
| **Shifa International Hospital, Islamabad.** | Dr Naveed Rashid, Site-PI | Infectious diseases | Phase-III | ---- |
| **National Hospital and Medical center, Lahore.** | Dr. Nadia Majeed, Site-PI | Infectious Diseases | Phase-III | **Site not approved for generalized trials.** |
| **The Central Park Teaching Hospital, Lahore.** | Dr. Muhammad Ahmed , Site-PI | Pulmonology | Phase-III | ----- |
| **Dow University of Health Sciences, Karachi** | Dr. Aziz Ullah Khan Dhiloo, Site-PI | Infectious Diseases | Phase-III | -------- |
| **Sindh Infectious Disease Hospital & research Center, Karachi.** | Dr. Muneeba Ahsan Sayeed, Site-PI | Infectious Diseases | Phase-III | ------- |
| **Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad.** | Dr. Tanveer Khaliq, Site-Pi | Surgeon | Phase-III | ----- |
| **Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi.** | Dr. Ume Sughra, National-PI | Epidemiologist | Phase-III | ------ |

**Primary & Secondary Objectives**

i. To categorize the effect of JT001 (VV116) compared to placebo on over all participant clinical status. **(Primary)**

ii. The secondary objectives are to categorize the effect and safety of JT001 (VV116) compared to placebo on;

a. Overall participant clinical status,
b. Covid-19 related hospitalization rate of non-hospitalized participants,
c. SARs-CoV-2 negative rate through day 7,
d. The plasma concentration of JT001 (VV116) and major metabolites when administered orally to participants (optional) &
e. Safety.

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. 05722831, dated 13th December, 2022. |
| 3 | Investigator Brochure (s) | English Language<br>Version 4.0 dated July 22, 2022. |
| 4 | Final protocol | Attached<br>Protocol Number JT001/VV116, Version 4.0 dated July 22, 2022.<br>**Protocol not signed by Sponsor/ PI.** |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached. |

| | | |
|---|---|---|
| | | **The ICF has been only designed for Ahga Khan Unversity Hospital. As per ICF Dr. Faisal Mehmood is PI while as per Form-II Dr. Ume Sughra is PI.** |
| 6 | List of participating countries | Argentina, Brazil, Columbia, India, Mexico, Pakistan, Philippines, Hong Kong, Nigeria |
| 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. | JT001 + placebo = 225 cartons.<br>Each carton contains 2 bottles.<br>Each Bottle Contain 20 tablets.<br>**Quantities to be imported are not justified.** |
| 9 | Sites of the trial | Agha Khan University, Karachi<br>Rehman medical Institute, Peshawar.<br>Maroof International Hospital, Islamabad.<br>Shifa International Hospitals Ltd, Islamabad<br>National Hospital and Medical center, Lahore. (**Site not approved for generalized CT**)<br>The Central Park Teaching Hospital, Lahore.<br>Dow University of Health Sciences, Karachi<br>Sindh Infectious Disease Hospital & research Center, Karachi.<br>Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad.<br>Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi. |
| 10 | Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members. | Agha Khan University, Karachi<br>Rehman medical Institute, Peshawar.<br>Maroof International Hospital, Islamabad. (Notification not as per ICH guidelines and Bio-Study Rules 2017)<br>Shifa International Hospitals Ltd, Islamabad.<br>National Hospital and Medical center, Lahore.(IRB Notification not attached.)<br>The Central Park Teaching Hospital, Lahore.<br>Dow University of Health Sciences, Karachi.<br>Sindh Infectious Disease Hospital & Research Center, Karachi.<br>Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad. (Notification not attached) |

| | | |
|---|---|---|
| | | Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi. |
| 11 | Approval of National Bio-ethics Committee (NBC) | Approved vide Ref: No.4-87/Covid-124/22/671 dated 24th November 2022.<br>Ref:No. 4-87/COVID-124/22/1063 dated January 26, 2023. |
| 12 | CV's of the Investigators | CVs of following (site-PI & national-PI) are attached.<br>Syed Faisal Mehmood at Agha Khan University, Karachi<br>Dr. Sajjad Ali at Rehman medical Institute, Peshawer.<br>Dr. Sajjad Naseer at Maroof International Hospital, Islamabad.<br>Dr. Naveed Rashid, Shifa International Hospitals Ltd, Islamabad<br>Dr. Nadia Majeed, National Hospital and Medical center, Lahore.<br>Dr. Muhammad ahmed, The Central Park Teaching Hospital, Lahore.<br>Dr. Aziz Ullah Khan, Dow University of Health Sciences, Karachi<br>Dr. Muneeba Ahsan Sayeed, Sindh Infectious Disease Hospital & research Center, Karachi.<br>Prof. dr. Tanveer Khaliq, Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad.<br>Dr. Ume Sughra, Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi. |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | Instead of GMP certificate, **Certification of cGMP compliance and statement of GMP certificate issued by Shangai Desano Bio-Pharmaceutical Company is attached.** |
| 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 (**16**)<br>Rehman medical Institute, Peshawer **(24)**<br>Maroof International Hospital, Islamabad.**(15-20)**<br>Shifa International Hospitals Ltd, Islamabad **(15)**<br>National Hospital and Medical center, Lahore. **(33)**<br>The Central Park Teaching Hospital, Lahore. **(12)**<br>Dow University of Health Sciences, Karachi **(10)**<br>Sindh Infectious Disease Hospital & research Center, Karachi **(12)**<br>Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad.**(30-35)**<br>Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi. **(15)** |

| | | |
|---|---|---|
| 19 | Name of Monitors & Clinical Research Associate | **Karachi:** Sadia Hashmi<br>**Islamabad:** Asjid Ali Arshad, Sidra Rashid<br>**Lahore:** Mahir ahmad, Hasina Sarwar, Muhammad Asif Mehmood. |
| 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. | Attached. |
| 22 | Duration of trial | 10 months (March 2023-December 2023) |
| 23 | Undertaking on Stamp paper | Attached. |

In the light of above, following shortcomings/ observations has been noticed.

i. Protocol not signed by Sponsor/ PI.
ii. The ICF has been only designed for Ahga Khan University Hospital.
iii. As per ICF Dr. Faisal Mehmood is PI while as per Form-II Dr. Ume Sughra is PI.
iv. Applied doses are 9984 tablets while as per calculation 8986(6912+2024 (30% extra)). Justification required for 1000 extra doses from calculation and 30% extra.
v. National Hospital and Medical center, Lahore is not approved CTS for generalized clinical trial.
vi. IRB notification of Maroof International Hospital, Islamabad is not as per ICH guidelines/ Bio-Study Rules 2017.
vii. IRB notification of National Hospital and Medical center, Lahore not attached.
viii. IRB notification of Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad not attached.
ix. GMP certificate not attached. Instead of GMP certificate, Certification of cGMP compliance and statement of GMP certificate issued by Shangai Desano Bio-Pharmaceutical Company is attached.
x. As per attached documents two manufacturer of the product have been mentioned Shangai Desano Bio-Pharmaceutical Company and 2Y-Biopharma, ltd.

**Decision: -**

*The CSC after detailed discussion and deliberation decided to defer the subject case for the fulfillment of following shortcoming;*

*i. Protocol not signed by Sponsor/ PI.*
*ii. The ICF has been only designed for Aga Khan University Hospital.*
*iii. As per ICF Dr. Faisal Mehmood is PI while as per Form-II Dr. Ume Sughra is PI.*
*iv. Applied doses are 9984 tablets while as per calculation 8986(6912+2024 (30% extra)). Justification required for 1000 extra doses from calculation and 30% extra.*
*v. National Hospital and Medical center, Lahore is not approved CTS for generalized clinical trial.*
*vi. IRB notification of Maroof International Hospital, Islamabad is not as per ICH guidelines/ Bio-Study Rules 2017.*
*vii. IRB notification of National Hospital and Medical center, Lahore not attached.*
*viii. IRB notification of Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad not attached.*

*ix. GMP certificate not attached. Instead of GMP certificate, Certification of cGMP compliance and statement of GMP certificate issued by Shangai Desano Bio-Pharmaceutical Company is attached.*

*x. As per attached documents two manufacturer of the product have been mentioned Shangai Desano Bio-Pharmaceutical Company and 2Y-Biopharma, ltd.*

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**AGENDA ITEM X:**

**TRANEXAMIC ACID (TXA) FOR REDUCINGPOSTPARTUM BLEEDING IN WOMEN WITH ANEMIA: AN INTERNATIONAL, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL (WOMEN-II TRIAL) (F. No.03-03/2019-DD (PS)**

**Request A**. The "TRANEXAMIC ACID (TXA) FOR REDUCINGPOSTPARTUM BLEEDING IN WOMEN WITH ANEMIA: AN INTERNATIONAL, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED TRIAL (WOMEN-II TRIAL)" was approved in July 2019 wherein the PI is Prof. Dr. Rizwana Chaudhary, Principal Scientist GIHD-STMU, Islamabad.

2. Prof. Dr. Rizwana Chaudhary, Principal Scientist GIHD-STMU submitted a letter 21.07.2022 wherein she has stated that she is thankful to DRAP members for supporting Woman 2 Trial. She has applied for drug import licence on 25th April 2022. As per requirement of the licensing department, she hereby applying for approval of quantities mentioned in import licence **application (80 drug boxes in total)**. She has attached the detailed report of previously imported drug boxes.

3. Applicant has provided list of Expired Drug Boxes at site/ Distribution Center, proof of destruction as site, proof drug destruction at PNCC. As per rule 8 (13) of Bio-Study Rules 2017 (13) The destruction of unused investigational products should be carried out after seeking approval from CSC which shall nominate officers to accompany during the process of destruction of investigational products". Applicant has destroyed without approval from CSC and also has not attached the prescribed fee under miscellaneous heading.

4. Accordingly, letter No.F.03-03/2019 DD (PS) dated 05th August 2022 was written to PI with following queries;

As per SRO 1047 (I)/2019, fee for miscellaneous applications is Rs. 25,000/- that has not been deposited with your application. Secondly, as per rule 8 (13) of Bio-Study Rules 2017 (13) The destruction of unused investigational products should be carried out after seeking approval from CSC which shall nominate officers to accompany during the process of destruction of investigational products" while as per this office record you have destroyed the products without approval of CSC. Therefore, it is advised to explain your position regarding queries in para 2 to proceed further in the matter please.

5. The reply from Dr. Rizwana Chaudhary in response to this office letter F.No. 03-03/2019 DD (PS) dated 5th August 2022 has been received, wherein she has submitted fee of Rs.25000/- and has submitted that;

"*Please accept our apology for the destruction of un-used Investigational product without seeking prior approval from CSC. The COVID -19 pandemic had adversely affected Woman Two Trial recruitment leading to the expiry of 2263 unused drug packs, along with another 232 packs received damaged at the trial sites. To sum up, 2495 drug packs were not used for enrolling eligible participants in Woman two trial, from the quantity approved for Importation. We are deeply regretful for not informing CSC in timely manner about the drug destruction, primarily because we were at that time in the process of shifting our center form Rawalpindi Medical University to Shifa- Tameer Millat*

*University Islamabad. However, in the future we would be more vigilant regarding IMP destruction and will follow the terms and conditions laid in Bio- Study Rules 2017.*

*1, being the lead investigator, hold the responsibility of drug destructions and ensure you that none of the expired drug packs were used outside the DRAP approved term and conditions and will never be done in the future. Our center follows the policy of abiding by all the International and local regulation, applicable on conduction of the clinical trials and will appreciate immense support in promoting clinical trial culture in country*"

6. Following is the summary of previously imported IMPs (Tranexamic Acid and Placebo) and its use.

IMPs imported……..525 Box (20 Packs) = 10,500 Packs
Packs damaged/ broken = 232 Packs
Packs destroyed due to expiry = 2263 Packs
**Packs Used (10,500- (232+2263)) = 8,005 Packs**

But the applicant has recruited total **8,359** subjects that needs clarification. Now the applicant has requested for 80 boxes (80 x 20 = 1600 packs). Further, GMP certificate and CoPP or Free Sale Certificate are required.

**Request B.** 1. The letter signed by National coordinator and Chief Investigator of the trial was submitted on 04.08.2022 wherein they have stated that **CTS Aziz Bhatti Shaheed Teaching Hospital, Gujrat is withdrawn** from the trial site, primarily because of low event rate.

2. The Prof. Dr. Rizwana Chaudhary on 7th September 2022 was requested to submit detailed progress report of said trial including SAEs on CIOMS form, complete activities carried out on the site under reference, trial subject follow up status.

3. In response to this office letter F. No. 03-03/2022 DD (PS) dated 7th September 2022, the applicant has attached following close out report signed by Llion Roberts, CTU Representative;

| | | | |
|---|---|---|---|
| **Trial Name** | Woman-2 | **Protocol No.** | ISRCTN62396133 |
| **Country** | Pakistan | **Site Name & Site ID** | Aziz Bhatti Shaheed Teaching Hospital (Site # 17) |
| **Investigator completing close out** | Dr. Shahida Husain Tarar | **No. of patient recruited** | 132 |
| **Visit Date** | N/A | **CTU Representative** | Llion Roberts |

| **Status** | **Task** | **Date Completed** | **Comments** |
|---|---|---|---|
| 1 | All CRF/data forms completed and returned to CTU | | |
| 2 | All data queries resolved | 05/08/2022 | |
| 3 | Site Close-out Monitoring Checklist completed by site and any required action completed and signed by CTU | 13/07/2022 | |
| 4 | All study drug accounted for | 27/06/2022 | |
| 5 | All study-related supplies that are no longer needed returned or destroyed (if applicable). | 13/07/2022 | |

| | | | |
|---|---|---|---|
| 6 | All AEs or SAEs reported at site | N/A | No AEs or SAEs reported at site |
| 7 | Any instances of emergency breaking of the blind appropriately documented. | N/A | No unblinding has occurred at site. |
| 8 | IRB/EC (both local and national if required) notified that the study has terminated at this site National regulatory authority notified that the study. | 15/06/2022 | LEC alerted |
| 9 | National regulatory authority notified that the study has terminated at this site. | | PNCC will inform once final notification sent. |
| 10 | Report submitted to the IRB. | N/A | |
| 11 | CTU copied on IRB correspondence. | 13/07/2022 | |
| 12 | Site files prepared for long-term storage. | 13/07/2022 | |
| 13 | PI confirmed that adequate archiving facilities of medical records is available. | 01/06/2022 | Confirmed in self-monitoring checklist. |
| 14 | All payments completed. | 19/07/2022 | PNCC confirmed in last weekly meeting |
| 15 | Archiving of Site Files arranged (insert details under comments). | 01/06/2022 | Stored in OPD at Aziz Bhatti Shaheed Teaching Hospital. |
| **Comments (cross-reference to the item number)**<br><br>**Note; Number of drug boxes sent to the site = 2117,2159,2185, 2202, 2214, 2231, 4020, 4154, 8102, 8142.**<br><br>**Note; Study report can only be submitted after the end of the trial.** | | | |

**Request C.** 1. The case is request from Prof. Dr Rizwana Chaudhri, Head of Translational Research Department Shifa Tameer-e-Millat University, Islamabad, where she has **requested the grant of approval for the amendments in the clinical trials of Tranexamic Acid (TXA)** for Reducing Postpartum Bleeding in Women with Anaemia: An International, Randomized, Double Blind, Placebo Controlled Trial (Women-II Trial). **F. No.03-03/2019-DD (PS)**

2 The application is submitted for the grant of approval for the following amendments,

a. The sample size has been increased from 10,000 to 15,000 participants to ensure that treatment benefits are not missed at the end of the treatment.
b. The overall end date changes to 31st October 2024 to allow for the recruitment of the additional 5000 participants.

3. The following amended documents have been enclosed with the application,

i. Processing fee deposit voucher of Rs.25000/- for Women 2 trail protocol amendment version 2.0.
ii. Updated Clinical trial protocol and trial protocol summary.
iii. English and Urdu versions of study information sheet, Patient information sheet and Consent forms.

iv. Appendices for the updated contact details of the trial coordinating team (appendix1), list of participating sites (appendix 7), updated list for the members of the trial steering committee (appendix 9), amended brief study information sheet and patient information sheet & consent form (appendix 3 & 4 respectively).
v. Updated women 2 trial patient poster both in English and Urdu versions.

By means of the extension of end date for the period of 2 years i.e. till 31st October 2024, version 2.0 (1.3 previously) and sample size increase in 5000 participants that is 15000 participants in total.

vi. Approval letter from "LSHTM Research Ethics Committee" of London School of Hygiene & Tropical Medicines. (Dated: 24th August, 2022)
vii. Approval letter from "National Bioethical Committee" for the period of one year, with the intimation that further continuation of the project shall be on the basis of progress report and a formal request for continuation. (Dated: 24th September 2022).
viii. Approvals form Local Ethics Committees for each recruiting site respectively for the amended protocol, along with the notification for the composition of these ethical committees and conflict of interest declaration forms (as mentioned below)

| **Recruiting sites** | **IRB/ERB approval** | **Notification** |
|---|---|---|
| Ayub Teaching Hospital Unit A, B and C | Approved (22-09-2022) | Attached |
| Bahawal Victoria Hospital (Unit I, II) | Approved (12-10-2022) | Attached |
| Bolan Medical Complex, Quetta (Unit I, II) | Approved (04-10-2022) | Not attached |
| Bolan Medical Complex (Unit III, IV) | Approved (04-10-2022) | Not Attached |
| Chandka Medical College, Shaheed Mohtarama Benazir Bhutto Medical University, Sheikh Zaid Hospital Larkana (Units I, II, III) | Approved (24-09-2022) | Attached |
| Civil Hospital Karachi (Units I and III) | Approved (22-10-2022) | Attached |
| Jinnah Hospital Lahore (Unit II) | Approved (06-10-2022) | Attached |
| Jinnah Post Graduate Medical Centre, Karachi (Wards 8 & 9) | Approved (07-10-2022) | Attached |
| MCH Centre PIMS, Islamabad (Units I, II) | Approved (24-10-2022) | Attached |
| Nishtar Hospital, Multan (Units I, II, III) | Approved (21-10-2022) | Attached |
| Sir Ganga Ram Hospital Lahore (Units I, II, | Approved | Attached |

| | | |
|---|---|---|
| III, IV) | (07-10-2022) | |
| | | |

1. It is

4. Following deficiencies have been observed in the submitted document.

i. Insurance of the subjects/participants undergoing clinical trials by the investigational unit, in case of profound risks likely to be observed during or after the trial.

**ii.** Dr.Ruqqia Sultana, principle investigator of Women 2 trial and also member of ethical review committee (ERC) at Ayub Teaching Hospital Abbottabad. She has issued notification of ERC five members with her signature including herself. She has also submitted that she has not participated in the meeting to avoid conflict of Interest. **Without her ERC is four-member committee that is not as per ICH-guidelines and Bio-Study Rules 2017. Further, composition of the ERC along with name and designation is required.**

iii. **ERC of M/s Fatima Jinnah Medical University, Lahore is not as per rule 9(2)(b) of the Bio-Study Rules 2017.**

**iv. Notification ethical review committee. Quaid-e-Azam Medical College, Bahawalpur is not as per ICH guidelines and Bio-Study Rules 2017.**

**v. ERC Notification of ethical review committee, Bolan Medical Complex (Unit 1-4) Quetta is not attached.**

vi. **Prof. Haleema Yasmin site PI at JPMC, Karachi is also member of IRB i.e conflict of interest. Notification of IRB is not as per ICH-Guidelines and Bio-Study Rules 2017.**

**vii. Designation of ERB members has not been mentioned in notification M/s Allama Iqbal Medical College, Jinnah Hospital, Lahore.**

**viii. Minutes of meeting of ERC of SMBBMU, Larkana is required to check the conflict of interest of Prof. Dr. Shahida Magsi.**

**ix. Minutes of meeting of ERC of Nishtar Medical University, Multan is required to check the conflict of interest of Prof. Dr. Mehnaz Khakwani.**

**x. ERB/IRB approval of M/s Benazir Bhutto Hospital, Rawalpindi, Services Institute of Medical Sciences, Lahore, Pak-Emirates Miltary College, Rawalpindi, Kohi Goth Women Hospital, Karachi and Shifa International Hospital is not attached.**

5. Applicant has not attached the valid GMP certificate, CoPP/ Free Sale Certificate with the application. Four countries i.e. Pakistan, Nigeria, Tanzania and Zamia have participated in the trial. Total recruitments till 21st September 2022 is 10,033 subjects. In Pakistan 8359, Nigeria 791, Tanzania 458 and Zamia 425 subjects has been recruited. We may ask the applicant to submit detailed progress report along with follow up to date.

The case was placed before CSC for its 36th meeting held on 21st November 2022 and was decided as follow;

*The CSC after detailed discussion and deliberation decided the various requests of Dr. Rizwana Chaudhry as follow:*

i. *The request to import IMPs (80 boxes) and destruction of IMPs without permission of CSC was discussed in details & the Committee decided & delegated its powers to the Chairman CSC to constitute an expert panel for verification/audit/reconciliation of previously imported IMPs.*
ii. *The Committee considered and acceded to the request for withdrawal of the Clinical Trial Site at Aziz Bhatti Shaheed Teaching Hospital Gujrat from the trial subject to the conditions that, applicant shall submit detailed progress report of said trial including AEs & SAEs, complete activities report carried out at the site signed by the site PI.*
iii. *The request for protocol amendments was deferred due to the following shortcomings:*
    a. *Insurance of the subjects/participants undergoing clinical trials by the investigational unit, in case of profound risks likely to be observed during or after the trial.*
    b. *Dr. Ruqqia Sultana, principle investigator of Women 2 trial and also member of ethical review committee (ERC) at Ayub Teaching Hospital Abbottabad. She has issued notification of ERC five members with her signature including herself. She has also submitted that she has not participated in the meeting to avoid conflict of Interest. Without her ERC is four-member committee that is not as per ICH-guidelines and Bio-Study Rules 2017. Further, composition of the ERC along with name and designation is required.*
    c. *ERC of M/s Fatima Jinnah Medical University, Lahore is not as per rule 9(2)(b) of the Bio-Study Rules 2017.*
    d. *Notification ethical review committee. Quaid-e-Azam Medical College, Bahawalpur is not as per ICH guidelines and Bio-Study Rules 2017.*
    e. *ERC Notification of ethical review committee, Bolan Medical Complex (Unit 1-4) Quetta is not attached.*
    f. *Prof. Haleema Yasmin site PI at JPMC, Karachi is also member of IRB i.e. conflict of interest. Notification of IRB is not as per ICH-Guidelines and Bio-Study Rules 2017.*
    g. *Designation of ERB members has not been mentioned in notification M/s Allama Iqbal Medical College, Jinnah Hospital, Lahore.*
    h. *Minutes of meeting of ERC of SMBBMU, Larkana is required to check the conflict of interest of Prof. Dr. Shahida Magsi.*
    i. *Minutes of meeting of ERC of Nishtar Medical University, Multan is required to check the conflict of interest of Prof. Dr. Mehnaz Khakwani.*
    j. *ERB/IRB approval of M/s Benazir Bhutto Hospital, Rawalpindi, Services Institute of Medical Sciences, Lahore, Pak-Emirates Military College, Rawalpindi, Koohi Goth Women Hospital, Karachi and Shifa International Hospital is not attached.*
    k. *GMP Certificate of IMPs along with CoPP/Free Sale Certificate is not provided.*
    l. *Four countries are participating in the trial. Till 21st September, 2022, 10033 Subjects has been recruited (In Pakistan 8359, Nigeria 791, Tanzania 458 and Zamia 425 subjects). Clarification is required for the number of subjects to be recruited in Pakistan.*

2. *Further, applicant was given one last opportunity to provide requisite documents within 15 days positively, failing which the application will be liable to be rejected.*

ln reference to CSC decision communicated vide this office letter No F.No.16-36/2022DO (PS) dated 25th of November 2022, the following response was submitted. The response to the queries/comments raised has been evaluated in tabulated form as following;

| Shortcoming/ Query | Reply of applicant | Comments |
|---|---|---|
| i. The request to import IMPs (80 boxes) and destruction of IMPs without permission of CSC was discussed in details & the Committee decided & delegated its powers to the Chairman CSC to constitute an expert panel for verification/audit/reconciliation of previously imported IMP,. | All the details of previously imported IMP were already shared with the Pharmacy Services Division of DRAP on 18th of July, 2022.Ihe conditions that led to the destruction of lMPs without permission of CSC along with a detailed apology were shared and accepted by the respected members of the CSC committee in its 36th meeting held on 21st of November, 2022.<br>To provide insight into the drug destruction, the COVID -19 pandemic had adversely affected Woman Two Trial recruitment leading to the expiry of 113 unused drug boxes, along with another 232 packs received | The panel comprising of Dr. Noor Muhammad Shah, Chairman CSC/ Director PS and Mr. Shafqat Hussain Danish has been constituted vide this office letter dated 12th |

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| | damaged at the trial sites. To sum up, a considerable amount of IMP was not used for enrolling eligible participants in Woman two trial, from the quantity approved for importation. We are deeply regretful for not informing CSC in timely manner about the drug destruction, primarily because we were at that time in the process of shifting our center form Rawalpindi Medical University to Shifa- Tameer e Millat University Islamabad. However, as discussed in the CSC meeting, all our sites are tertiary care public sector hospitals and follow the governmental policy of drug handling and destruction. ln addition there is no chance of illegitimate usage of our trial drug which is Tranexamic acid (TXA). Tranexamic acid is freely available in the country and has well established safety profile with no detrimental health effects including carcinogenesis. ln the future we would be more vigilant regarding IMP destruction and will follow the terms and conditions laid in Bio-Study Rules 2017. | December 2022. |
| ii. The Committee considered and acceded to the request for withdrawal of the Clinical Trial Site at Aziz Bhatti Shaheed Teaching Hospital Gujrat from the trial subject to the conditions that, applicant shall submit detailed progress report of said trial including AEs & SAEs, complete activities report carried out at the site signed by the site PI. | Please find attached the detailed progress report of Woman two trial including AEs & SAEs, along with complete activities report carried out at Aziz Bhatti Shaheed Teaching Hospital Gujrat signed by the site Pl and LSHTM representative in **Appendix l.** | Appendix I attached. |
| iii. The request for protocol amendments was deferred due to the following shortcomings: | iii. The request for protocol amendments was deferred due to the following shortcomings | |
| a. Insurance of the subjects/participates undergoing clinical trials by the investigational unit, in case of profound risks likely to be observed during or after the trial. | a. We as a clinical **trialist** consider the participant benefit and safety beyond any other factor and have a detailed insurance policy in place. The initial insurance certificate was part of the original application of Woman Two Trial submitted to DRAP in 2019. The updated insurance certificate was shared with DRAP Pharmacy division on 4th of February, 2021. DRAP official receipt along with updated insurance certificate is attached in Appendix Il for reference. | The insurance summary is attached. |
| b. Dr. Ruqqia Sultana, principle investigator of women 2 trial and also member of ethical review committee (ERC) at Ayub Teaching Hospital Abbottabad. She has | Prof Ruqqia Sultana was informed about the DRAP guidelines of constitution of local ethics committee as per rule 9 of the Bio-study rules 2017. She requested the Vice Chancellor and the Dean at Ayub Teaching Hospital Abbottabad for reconstitution of the ethics committee as per DRAP requirement. Woman | Committee notification dated 12.10.2022, IRB approval dated 07.12.2022 |

| | | |
|---|---|---|
| issued notification of ERC five members with her signature including herself. She has also submitted that she has not participated in the meeting to avoid conflict of interest. Without her ERC is four-member committee that is not as per ICH-guidelines and Bio-Study Rules 2017. Further, composition of the ERC along with name and designation is required. | Two Trial Protocol Amendment version 2.0 was again presented and discussed before the members of the newly appointed ethics committee. Kindly find attached the notification of revised composition of ethics committee, minutes of meeting and conflict of interest declaration by Prof Ruqqia Sultana. | along with minutes of meeting of IRB is attached. Dr. Ruqqia Sultana has not participated in meeting to avoid conflict of interest. |
| c. ERC of M/s Fatima Jinnah Medical University, Lahore is not as per rule 9(2)(b) of the Bio-Study Rules 2017. | Please find attached the notification of local ethics committee of Fatima Jinnah Medical University, Lahore in line with ICH guidelines and Biostudy rules 2017 in Appendix lV. | Approval along with members who attended the meeting is attached. |
| d. Notification ethical review committee. Quaid-e-Azam Medical College, Bahawalpur is not as per ICH guidelines and Bio-study Rules 2017. | Please find attached the notification of local ethics committee of Quaid-e-Azam Medical College, Bahawalpur, in line with ICH guidelines and Biostudy rules 2017 in Appendix V. | Notification of new members attached. |
| e. ERC Notification of ethical review committee, Bolan Medical Complex (Unit l-4) Quetta is not attached. | Please find attached the notification of ethical review committee at Bolan Medical Complex Quetta in Appendix VI. | |
| f. Haleema Yasmin site Pl at JPMC, Karachi is also member of IRB i.e. conflict of interest. Notification of IRB is not as per lCH-Guidelines and Bio-Study Rules 20 I 7. | Please find attached the notification of IRB as per ICH guidelines and Biostudy rules2Ol7, minutes of meeting and conflict of interest declaration by Prof Haleema Yasmin in Appendix Vll. | Minutes of IRB enclosed. |
| g. Designation of ERB members has not been mentioned in notification M/s Allama lqbal Medical College, Jinnah Hospital, Lahore. | Designation of ERB members of M/s Allama lqbal Medical College, Jinnah Hospital, Lahore is mentioned and highlighted in the notification attached in Appendix VIll. We would really like to know if CSC is interested in any other details. | Attached. |
| h. Minutes of meeting of ERC of SMBBMU, Larkana is required to check the conflicts of interest of Prof. Dr. Shahida Magsi. | Please find attached the minutes of the meeting of ERC of SMBBMU, Larkana, along with conflict of interest declaration from the Pl, Prof Dr. Shahida Magsi, in Appendix lX. | Minutes attached. |
| i- Minutes of meeting of ERC of Nishtar Medical University, Multan is required to check the conflict of interest of Prof, Dr. Mehnaz Khakwani. | Please find attached the minutes of the meeting of ERC of Nishtar Medical University, Multan, along with conflict of interest declaration from the Pl, Prof Dr Shahida Magsi in Appendix X. | Minutes attached. |

| | | |
|---|---|---|
| j. ERB/IRB approval of M/s Benazir Bhutto Hospital, Rawalpindi, Services Institute of Medical Sciences, Lahore, Pak Emirates Military College, Rawalpindi, Koohi Goth Women Hospital, Karachi and Shifa International Hospital is not attached | The following sites were closed<br>o Benazir Bhutto Hospital, Rawalpindi,<br>o Services lnstitute of Medical Sciences, Lahore,<br>o Pak Emirates Military College, Rawalpindi,<br>o KoohiGoth Women Hospital, Karachi.<br>The official notification of closure was submitted to DRAP pharmacy division on L't April, 2022. Please find the official DRAP receipt in Appendix XI.<br>Regarding Shifa International hospital, Department of Translational Research has been approved by<br>Institutional Review Board and Ethics committee of Shifa International Hospital for the conduction of clinical trials under the supervision of Prof Rizwana Chaudhri. This approval has already been submitted to the DRAP Pharmacy division. Please find attached in Appendix Xll. | IRB approval of Shifa Hospital attached. |
| k. GMP Certificate of IMPs along with CoPP/Free Sale Certificate is not provided | Please find attached the GMP certificate along with the extension granted by MHRA till end of year 2022 in Appendix Xlll. The new GMP certificate will be provided after it will be issued in January, 2023. | GMP certificate attached while CoPP/ Free sale certificate not attached. |
| Further applicant was given one last opportunity to provide requisite documents within 15 days positively, failing which the application will be liable to rejected. | | |

l. **Four countries are participating in the trial. Till 21st September, 2022, 10033 Subjects has been recruited (in Pakistan 8359, Nigeria 791, Tanzania 458 and Zambia 425 subjects). Clarification is required for the number of subjects to be recruited in Pakistan.**

As already shared with the members of respected CSC, predecessor of Woman two trial, the Woman Trial, was conducted in 193 hospitals across the world in 21 countries. ln the Woman Trial, we randomly assigned women to receive either 1 g intravenous tranexamic acid (TXA) or matching placebo in addition to usual care. 20,060 women were enrolled and randomly assigned to receive tranexamic acid (n=10051) or placebo (n=10 009), of whom 10035 and 9985, respectively, were included in the analysis.

The results of the trial are phenomenal and it proved that Tranexamic acid reduces 30 percent deaths due to bleeding in women with post-partum hemorrhage with no adverse effects. Pakistan was the second highest recruiter in the trial with 5282 patients randomized. As a result of this trial, TXA became the first line treatment for the management of PPH as per WHO recommendations in 2O17.

The best performing sites were selected for Woman Two Trial and we are proud to share that most of them are from Pakistan. Not only our sites in Pakistan are conducting the trial meticulously but also are very proficient in collecting and uploading the trial related data. This leads to more patients being randomized in Pakistan as compared to other participating countries. ln protocol amendment 2.0, the overall sample size allocated to Pakistan is 12000 patients, based on the incidence of moderate and severe anemia and birth and recruitment rate observed in the trial to date. This number is inclusive of the patients already recruited in the trial by Pakistan.

We also recognize the role of regulatory and ethics bodies in approving the Woman two trial and their support throughout. We humbly request the CSC that considering the paramount importance of our trial to Woman health; please provide us approval on priority basis. We have reached the current level

of success with your support and would request the same in future. We have established a dedicated network of researchers across the country and have employed forty-six research fellows to carry out trial related tasks. A delay in obtaining approval would jeopardize the future of research fellows with huge financial implications for the sponsor. The sponsor might consider the withdrawal of trial from our country altogether, making the research landscape gloomier for coming generations.

**Aziz Bhatti Shaheed Teaching Hospital Site Progress and Equity Report**

SECTION A: TRIAL INFORMATION

| | |
|---|---|
| Full Title of study: | Tranexamic acid for the prevention of postpartum bleeding in women with anaemia: an international, randomized, double blind, placebo-controlled trial |
| Short Title: | World Maternal ANtifibrinolytic 2 trial |
| Trial Acronym: | WOMAN.2 |
| Protocol Number: | ISRCTN62396133 |
| ClinicalTrials.gov ID: | NCT03475342 |

SECTION B: SITE INFORMATION

| | | | |
|---|---|---|---|
| Name of site: | Aziz Bhatti Shaheed Teaching Hospital (017) | | |
| Reason/s for completing the report | Site Close Out | | |
| Name of Principal investigator | Dr Shahida Husain Tarar | | |
| No of patients screened at the site | 137 | No. of patients randomized at the site | 132 |
| No. of serious adverse events (SAEs)reported in this period (see Section E for details of any event) | 0 | No. of suspected unexpected serious adverse reactions (SUSARS) reported in this period (see Section E for details of any event) | 0 |

SECTION C: BASELINE CHARACTERSTICS OF PARTICIPANTS RANDOMIZED AT SITE

| | | | | |
|---|---|---|---|---|
| 1 | Age (mean) | 28.1 | | |
| 2 | Gravity (Mean) | 3.6 | | |
| 3 | Parity inclusive of the current pregnancy (Mean) | 3.4 | | |
| 4 | Gestational age (Mean) | 37.2 | | |
| | | | Number | % |
| 5 | Participant with previous history of PPH | Yes | 1 | 0.8 |
| | | No | 130 | 98 |
| | | Unknown | 1 | 0.8 |
| 6 | Diabetes in the current pregnancy | None | 131 | 99.2 |
| | | Type-1 | 0 | -- |
| | | Type-2 | 0 | -- |
| | | Gestational | 1 | 0.8 |
| 7 | Participants with APH in the current pregnancy | Yes | 4 | 3 |
| | | No | 128 | 97 |
| 8 | Hypertensive disease in the pregnancy | None | 126 | 95.5 |
| | | Pre-eclampsia | 0 | -- |
| | | Eclampsia | 0 | -- |
| | | PIH | 6 | 4.5 |
| | | Pre-existing Hypertension | 0 | -- |
| 9 | Placental Abnormalities | None | 128 | 97 |
| | | Abruption | 4 | 3 |
| | | Previa | 0 | -- |

| | | | | |
|---|---|---|---|---|
| | | Accrete | 0 | -- |
| | | Increta | 0 | -- |
| | | Percreta | 0 | -- |
| 10 | Polyhydramnios | Yes | 0 | -- |
| | | No | 132 | 100 |
| 11 | Induction of Labour (Current Pregnancy) | Yes | 9 | 6.8 |
| | | No | 123 | 93.2 |
| 12 | Augmentation of Labour | Yes | 1 | 0.8 |
| | | No | 131 | 99.2 |
| 13 | Type of Delivery | Spontaneous vaginal | 132 | 100% |
| | | Assisted delivery | 0 | -- |
| 14 | Baby weight at birth (mean) | 2.83kg | | |
| 15 | Condition of baby | Alive | 127 | 93.4% |
| | | Dead | 9 | 6.6 |
| 16 | Any Birth Canal Trauma | None | 124 | 93.9% |
| | | Perineal | 4 | 3% |
| | | Vaginal | 1 | 0.8% |
| | | Cervical | 3 | 2.3% |

SECTION D: OUTCOME CHARACTERISTICS OF PARTICIPANTS RANDOMISED AT SITE

| | | | | |
|---|---|---|---|---|
| 1 | The participants diagnosed with PPH | Yes | 5 | 3.8% |
| | | No | 126 | 96.2% |
| 2 | Average blood loss of participants diagnosis with PPH (ml) | 688ml | | |
| 3 | Hemodynamic instability | Yes | 1 | 0.8 |
| | | No | 130 | 99.2 |
| 4 | Primary Cause of PPH | Atony | 2 | 40 |
| | | Placental implantation Abnormalities | 0 | -- |
| | | Tears | 2 | 40 |
| | | Retained Placenta tissue | 0 | -- |
| | | Uterine rupture | 0 | -- |
| | | Unknown | 1 | 20 |
| | | Others | 0 | -- |
| 5 | Other causes of PPH | None | 5 | 100 |
| | | Atony | 0 | -- |
| | | Placental implantation Abnormalities | 0 | -- |
| | | Tears | 0 | -- |
| | | Retained Placenta tissue | 0 | -- |
| | | Uterine rupture | 0 | -- |
| | | Unknown | 0 | -- |
| | | Others | 0 | -- |
| 6 | Intervention given for PPH | Oxytocin | 4 | 3.1 |
| | | Ergometrine | 0 | -- |
| | | Carbeton | 0 | -- |
| | | Prostaglandin | 0 | -- |
| | | Misoprostol | 6 | 4.6 |

| | | | | |
|---|---|---|---|---|
| | | Non- Trial TXA | 3 | 2.3 |
| | | Perineal suture | 37 | 28.3 |
| | | Cervical suture | 3 | 2.3 |
| | | Perineal and Vaginal packing | 2 | 1.5 |
| | | Uterine tamponade | 0 | -- |
| | | Bimanual Compression | 0 | -- |
| | | External Aortic Compression | 0 | -- |
| | | Non- pneumatic anti shock garments | 0 | -- |
| | | Removal of placenta and placental fragments | 0 | -- |
| | | Uterine compression suture | 0 | -- |
| | | Arterial ligation | 0 | -- |
| | | Hysterectomy | 0 | -- |
| | | Laparotomy | 0 | -- |
| | | Any Other | 0 | -- |
| 7 | Complication (Prespecified) | Pulmonary Embolism | 0 | |
| | | Deep Venus Thrombosis | 0 | -- |
| | | Myocardial infraction | 0 | -- |
| | | Cardiovascular dysfunction | 1 | 0.8 |
| | | Respiratory dysfunction | 1 | 0.8 |
| | | Renal dysfunction | 0 | -- |
| | | Coagulation/ Hematologic Dysfunction | 1 | 0.8 |
| | | Hepatic dysfunction | 0 | -- |
| | | Neurological dysfunction | 1 | 0.8 |
| | | Sepsis | 0 | -- |
| 8 | Condition of the participant at Discharge | Alive and discharged home | 132 | 100 |
| | | Alive and shifted to another hospital | 0 | -- |
| | | dead | 0 | -- |
| | | lf dead cause/s of death | N/A | -- |

FR (page 1675-1685) is another request from Dr. Rizwana Chaudhary wherein she has stated that We congratulate you for taking charge as Director, Division of Pharmacy Services, DRAP and looking forward to working with you. We are extremely grateful to DRAP Pharmacy Division for reviewing the Woman two trial protocol amendment version 2.0 application, submitted to DRAP Pharmacy Services Division, on 27th of October, 2022. However, some comments/queries were raised by the Clinical Studies Committee (CSC), in its 36th meeting held on 21st of November, 2022. These queries were communicated to us in a letter reference **No F. No 16-36/2022 DD (PS)** dated **25th of November 2022**. The response to above letter was submitted on 12th of December, 2022. Please note that the Woman Two Trial Protocol amendment version 2.0 has already been approved by the National Bioethics committee of Pakistan (NBC) on 27th of September, 2022 and also by the local ethics committees of all our recruiting sites. We are only waiting for the DRAP approval for resuming trial recruitment.

She also wrote that in the same meeting, CSC constituted an inspection panel for verification/audit/reconciliation of previously imported IMPs and we were informed officially about it through a letter dated 12th of December, 2022. We were directed to coordinate with the inspection panel members for the finalization of inspection schedule. However, so far we are still waiting for the inspection to be conducted. Since your joining as Director Pharmacy Services, we are requesting to do necessary facilitation in scheduling visit or otherwise if it is appropriate and acceptable please do consider waiving off the inspection visit altogether, if the DRAP regulations permit.

She also submitted that just to bring into your kind notice that the Woman Two trial is a multicenter Trial sponsored by London School of Hygiene and Tropical Medicine (LSHTM). The trial is being conducted at sixteen tertiary care hospitals all in the public sector. With the support of LSHTM, we have established a dedicated network of researchers across the country and have employed forty-six health professionals as research fellows to carry out trial related tasks. However, unfortunately the Woman Two trial is practically at halt for last three months. A delay in obtaining timely approval would jeopardize the future of research fellows

along with immense financial implications for the sponsor. In the current prevailing situation, the sponsor might consider the withdrawal of trial from our country altogether, as they would not be able to provide salaries for the research fellows for indefinite period of non-working. Considering the prevailing economic conditions of our country, this would be very unfortunate and will make the research landscape gloomier for coming generations.
At the end it has been requested that considering the paramount importance of our trial for women's health, please do consider our request for the necessary facilitation. We have reached the current level of success with DRAP support and would request the same in future (the official correspondence is also attached with application).

Applicant has addressed the shortcomings/ queries communicated by tis office letter F.No. 16-36/2022 dated 25 November, 2022, except CoPP/ Free sale certificate. Applicant has also been requested for exemption of inspection. The inspection was decided by the CSC in 36th CSC meeting and powers were delegated to Chairman CSC for constitution of panel and accordingly following panel was constituted;

i. Dr. Noor Muhammad Shah, Chairman CSC/ Director Division of Pharmacy Services-DRAP
ii. Shafqat Hussain Danish (Coordinator), Assistant Director, Division of Pharmacy Services-DRAP, Islamabad.

The panel has inspected the premises but has not submitted inspection report yet.

**Decision: -**

*The CSC after detailed discussion and deliberation and after reviewing the IRB/ NBC approvals decided as follows:*

*a. to approve the amended protocol number* SRCTN62396133 *version 2.0.*
*b. to direct the National PI to report to the Division of Pharmacy services for all the Adverse Events and measures taken for safety and wellbeing of the subjects.*
*c. Advised that panel will submit the verification report as decided in 36th meeting for the consideration of CSC.*
*d. The Chairman will approve the quantity of IMPs to be imported when applied by the applicant.*

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**AGENDA ITEM XI:**

**AN INTERNATIONAL RANDOMIZED TRIAL OF ADDITIONAL TREATMENTS FOR COVID-19 IN HOSPITALIZED PATIENTS WHO ARE ALL RECEIVING THE LOCAL STANDARD OF CARE. TRIAL SHORT TITLE: SOLIDARITY PLUS TRIAL.F.No.03-81/2021 DD (PS)**

The case is from Dr. Aun Raza consultant physician infectious diseases of M/s Shaukat Khanum Memorial Cancer Hospital and research Center, Lahore, dated 20th September 2021, wherein he has applied for approval/ registration of clinical trial titled **"An international randomized trial of additional treatments for covid-19 in hospitalized patients who are all receiving the local standard of care. Trial short title: solidarity plus trial." Using Inj. Artisunate, Imatinib and Infliximab.**

2. After initial scrutiny, following mandatory pre-requisite may kindly be requested from applicant for further processing the application.

i. Prescribed fee as per S.R.O 1047 (I)/2019 dated 12th September, 2019.

ii. Clarification whether it is a new trial or amendment in already applied trial i.e. an international randomized trial of additional treatments for COVID-19 in hospitalized patients who are all receiving the local standard of care. Solidarity trial using Chloroquine or Hydroxychloroquine, Lopinavir plus ritonavir and interferon beta.

3. After evaluation of your reply and documents/information furnished on the matter in response to this division letter dated 01st December, 2021, it is requested to submit application on Form-II as fresh application

along with all pre-requisite as required under Bio-Study Rules, 2017 due to following reasons vide letter dated 6th January 2022.

i. In Solidarity Trial drugs/IMPs to be used are Hydroxychloroquine, Remdesivir, Lopinavir/Ritonavir and Interferon whereas in Solidarity Plus trial different drugs/IMPs i.e. Artisunate, Imatinib and Infliximab are being used as compared to Solidarity Trial which tantamount to major change in trial/study.

ii. Title of trial is different i.e. Solidarity Trial has been changed to Solidarity Plus Trial.

iii. Protocol of the trial is completely changed.

iv. The last version in Solidarity Trial is 10.0, if we consider it as amendment next version must be 10.1 but in Solidarity Plus Trial Protocol version 1.0 has been drafted afresh supporting it to be a new trial/study.

v. As per WHO ERC / COVID-19 Review Summary – Approval submitted by applicant it is also not clearly mentioned that this is an amendment in Solidarity Trial. However, study/trial protocol ID are different which also indicate the trial under reference a new trial.

4. In view of above and also agreed on telephonic discussion in detail with Dr. Sadia representative of applicant, it is therefore advised to apply on prescribed Form-II along with other pre-requisites including prescribed fee so that your application can be evaluated for further processing and its placement before the Competent Forum i.e. CSC for its consideration.

5. the applicant Dr. Aun Raza consultant physician infectious diseases of M/s Shaukat Khanum Memorial Cancer Hospital and research Center, Lahore, forwarded through **what's app**, wherein he has enclosed the copy of Form-II for approval/ registration of clinical trial titled **"An international randomized trial of additional treatments for covid-19 in hospitalized patients who are all receiving the local standard of care". (Trial Acronym: Solidarity Plus Trial)** along with copy of fee challan slip No.256391126292 dated 11.01.2022.

6. The already submitted application has been evaluated in the light of newly submitted Form-II as followings:

7. The details of evaluation as per checklist provided in Bio-Study Rules 2017 are as followings;

| S. No. | Document | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-II | Attached |
| 2 | Fee | copy of fee challan slip No.256391126292 dated 11.01.2022. |
| 3 | Investigator Brochure (s) | SmPC attached instead of investigator Brochure. |
| 4 | Final protocol | Attached. |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached |
| 6 | List of participating countries | 52 countries around the world in collaboration with WHO |
| 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. | Artesunate 850 vials<br>Imatinib 600 Tablets<br>Infliximab 160 vials |

| | | |
|---|---|---|
| 9 | Site of the trial | Shaukat Khanum Memorial Cancer Hospital and research Center, Lahore.<br><br>Pakistan Institute of Medical Sciences (PIMS) Islamabad.<br><br>Shifa International Hospital, Islamabad.<br><br>Agha Khan University Hospital AKUH, Karachi.<br><br>Indus Hospital, Karachi. |
| 10 | Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members. | IRB/ERC approval from Shaukat Khanum Memorial Cancer Hospital and research Center, Indus Hospital, Shifa International Hospital, as amended approval in solidarity trial (Solidarity plus) is attached. Protocol number is the same. Approval from Shaheed Zulfiqar Ali Bhutto medical university for Solidarity plus trial is attached.<br>**Only the composition of IRB of SKCH&RC is attached.**<br>**IRB approval of agha Khan hospital not attached.** |
| 11 | Approval of National Bio-ethics Committee (NBC) | **An international randomized trial of additional treatments for covid-19 in hospitalized patients who are all receiving the local standard of care". (Trial Acronym: Solidarity (covid-93)** is **a**ttached |
| 12 | CV's of the Investigators | CVs of Dr. Aun Raza, Dr. Faisal Sultan, Salma Muhammad Abbas, Dr. Shahzeb Khan, Dr. Naseem Akhtar, Dr. Ejaz A. Khan, Dr. Nosheen Yasir, Dr. Syed Faisal Mehmood, Dr. Samreen Sarfraz are attached. |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | CoA & GMP certificate for Artisunate of IPCA Laboratory, India is attached.<br>CoA & GMP certificate for Imatinib of Lec pharmaceutical, A Sandoz company, Poslovna is attached.<br>CoA & GMP certificate for Infliximab of Jansen, Cilag AG, Switzerland is attached.<br>**COPP or Free Sale Certificate not attached.** |
| 14 | Pre-clinical/clinical safety studies | Applicant submitted that its available in SmPC. |
| 15 | Summary of Protocol | Trial Standard Operating Procedure and appendix attached. |
| 16 | Summary of Investigator Brochure | SmPC attached |
| 17 | Adverse Event Reporting Form | Attached. |
| 18 | No of patients to be enrolled in each center. | Around 120 patients |

| | | |
|---|---|---|
| 19 | Name of Monitors & Clinical Research Associate | Clinical Trial Unit of the University of Bern will conduct the global monitoring. Trial Steering Committee and its Executive group, WHO Trial center, Geneva and Global Data and Safety monitoring committee etc. will monitor. |
| 20 | Evidence of registration in country of origin. | SmPC attached. |
| 21 | Copy of registration letter (if registered in Pakistan) | IMPs are to be imported. |
| 22 | Sample of label of the investigational product / drug. | Label of Artesunate (Larinate) & Infliximab (KitNumb) is attached.<br>Label of Imatinib is not Attached. |
| 22 | Duration of trial | One year |
| 23 | Undertaking on Stamp paper | Not provided. |

8. This trial will be carried out in collaboration with WHO and is being managed by R & D blueprint team at WHO Headquarters, Switzerland. Trial governance will be at following levels:

i) **Trial steering Committee**- this will govern the conduct of trial in accord with the agreed international protocol, amended as necessary during the study. The National PI would be part of this committee.

ii) **Executive Group of steering Committee**- For practically a smaller executive group of about 5-9 members of this committee will be setup in consultant with WHO to confer electronically at frequent intervals with WHO to ensure trial steering committee is appropriately informed and consulted.

iii) **WHO Trial Center (Geneva)**- this will be responsible for the conduct of trial and remote central monitoring of collected data.

iv) **Global Data and Safety Monitoring Board-** this independent committee will examine confidential interim analysis of safety and efficacy, reporting them to executive group only if DSMC consider them likely to require publication or change in the conduct of trial.

9. In the light of above scrutiny and discussion of Secretary CSC with chairman CSC, the case has been placed before CSC in its meeting held on 13.01.2022 (as its international trial in collaboration with WHO).

10. Dr. Aun Raza, the applicant / PI of the study also joined the meeting on line through Zoom and presented his case before the CSC.

***Decision:***

*"The CSC after detailed discussion and deliberation decided to approve the trial at the following three sites subject to fulfilment of shortcomings as notified to the applicant during his presentation of the case:*

*i. M/s Shaukat Khanum Memorial Cancer Hospital and research Center, Lahore.*
*ii. M/s Shifa International Hospital, Islamabad.*
*iii. M/s Indus Hospital Karachi."*

11 Request from Shaukat Khanum Hospital and Research Center, Lahore wherein they have requested for the inclusion of following two Clinical Trial Sites as applied in initial application in already ongoing trial.

i. Shaheed Zulifqar Ali Bhutto Medical University, Islamabad.
ii. Agha Khan University Hospital, Karachi.

12. On evaluation it is submitted that the case was placed before CSC in its 34th meeting held on 13th January 2022 and the Committee has approved the trial for 3 sites however there were deficiencies regarding below mentioned sites, Now the applicant has submitted the following deficient documents:-

i. IRB approval of Shaheed Zulifqar Ali Bhutto Medical University, Islamabad.
ii. IRB approval of Agha Khan University Hospital, Karachi.
iii. Copy of Clinical Trial Site License of Shaheed Zulifqar Ali Bhutto Medical University, Islamabad.
iv. Copy of Clinical Trial Site License of Agha Khan University Hospital, Karachi

13. The case was placed before CSC in its 35th meeting held on 13th October, 2022 & the Committee decided the case as follows:

*The CSC after detailed discussion and deliberations decided to defer the case for further deliberation & due to paucity of time.*

14. The case was placed before the CSC in its 36th meeting 21st November 2022 & the Committee decided the case as follows:

*The CSC after detailed discussion and deliberations approved the addition of Aga Khan University Hospital Karachi to act as a CTS for Clinical Trial titled, "An international randomized trial of additional treatments for COVID-19 in hospitalized patients who are all receiving the local standard of care. Trial short title: solidarity plus trial."*

*Further, it was decided that, applicant will clarify that, whether they intend to include CTS situated at PIMS or SZAB Medical University, Islamabad. The applicant will submit a fresh request with permission of the Head of the institution along with clarification at earliest but not later than 30 days.*

15. The decision of CSC was communicated vide this office letter F.No.16-36/2022 DD (PS) dated 25th November 2022 and Dr. Aun Raza has submitted response to this letter wherein he has stated that we were directed to provide clarification whether PIMS will be acting as clinical trial site (CTS) for the above mentioned clinical study or SZAB Medical university. Please be informed that we have received a letter from registrar SZAB Medical University which states that the trial will be conducted at SZAB Medical University, a DRAP approved CTS. Applicant has also attached the letter issued by registrar.

**Decision: -**
*The CSC considered the request of the applicant and decide to approve the CTS situated at SZAB Medical University, Islamabad, for the subject mentioned trial. The CSC further directed the applicant to submit up dated progress report of the clinical trial (Pakistan and other participating countries).*

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**AGENDA ITEM XII:**

**APPLICATION FOR RENEWAL OF LICENSE TO ACT AS CENTER, CLINICAL TRIAL SITE FOR PHASE I, II, III &IV, FROM SHIFA CLINICAL RESEARCH CENTER, ISLAMABAD. F.No.15-14/2019-DD (PS).**

The case is the request from Dr. Ayaz Mir, Director, Shifa Clinical Research Center (SCRC), Islamabad, wherein he has enclosed application for renewal of licence for CTU (licence No. CTS-0026) situated at Shifa Clinical Research Center, Shifa International Hospital, Islamabad. The

application is on Form-III of Bio-study Rules 2017 along with fee of Rs. 100,000/ deposited vise slip number 5886037321 dated 23.12.2022.

2. The application has been evaluated below in tabulated form according to pre- requisites as mentioned in Form-III of the Bio-Study Rules 2017.

| S. No. | Required Documents / Information | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-I of The Bio-Study Rules 2017. | Attached. |
| 2 | Prescribed processing fee | Rs. 100,000/ deposited vise slip number 5886037321 dated 23.12.2022 |
| 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 Incorporation issued by security exchange Commission of Pakistan is attached. |
| 4 | Details of premises including layout plan of the site. | Layout plan attached. |
| 5 | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | List attached. |
| 6 | Names and qualifications of the management. | Attached. |
| 7 | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | Not attached. |
| 8 | Undertaking on stamp paper | Attached. |

3. The Application is for renewal of licence for CTS for phase I, II, III & IV. In the case it is proposed that panel for inspection may be constituted as per previous practice

**Decision: -**
*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.*

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**AGENDA ITEM XIII:**

**APPLICATION FOR LICENSE TO ACT AS TRIAL SPECIFIC (PHASE-III) CLINICAL TRIAL SITE FROM ONCOLOGY DEPARTMENT, ALLAMA IQBAL MEDICAL COLLEGE/ JINNAH HOSPITAL, LAHORE. (F.No.15-24/2023 DD (PS).**

The case is an application from Dr. Kausar Bano, CNIC No. 35201-1344676-4, Associate Professor, Head of Department of Oncology, Jinnah Hospital, Lahore, wherein she has

applied to act as Clinical Trial Site for phase III for clinical trial/study tilted as "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". The application is on Form-I of the Bio-Study Rules 2017 with prescribed fee of Rs. 100,000/- submitted vide slip No.75048268589 dated 22nd December 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 | Rs. 100,000/- submitted vide slip No.75048268589 dated 22nd December 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). | Public Sector Tertiary Care Hospital working under Government of the Punjab.<br>Punjab Healthcare Commission **Regular License** attached that was valid upto 10th November 2022. |
| 4 | Details of premises including layout plan of the site. | Layout plan attached. |
| 5 | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | Department wise equipment list attached. |
| 6 | Names and qualifications of the above sections along with their staff. | Following staff list along with their CVs attached.<br>Dr. Kausar Bano, Associate Professor,<br>Dr. Fareeha Sheikh, Senior Registrar,<br>Misbah Shahid, Pharmacist,<br>Shama Amen, Nurse,<br>Mohammad Abdullah, Research Coordinator. |
| 7 | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | List of Allied Facilities, Waste Management Agreement and SOP for emergency handling attached. |
| 8 | Undertaking on stamp paper | Attached. |

3. In the light of above, it is submitted that Allama Medical College/ Jinah Hospital is public sector organization working under Government of the Punjab. Jinnah Hospital, Lahore is the tertiary care hospital. The Licence issued by the Punjab Healthcare Commission was valid upto 10th November 2022. The applicant has applied for phase III for trial study "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".

**Decision: -**

*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.*

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**AGENDA ITEM XIV:**

**APPLICATION FOR LICENSE TO ACT AS TRIAL SPECIFIC (PHASE-III) CLINICAL TRIAL SITE FROM ONCOLOGY DEPARTMENT, KING EDWARD MEDICAL UNIVERSITY/ MAYO HOSPITAL, LAHORE. (F.No.15-25/2023 DD(PS))**

The case is an application from Dr. Muhammad Abbas Khokhar, CNIC No. 35201-1344676-4, Associate Professor/ Head of Department of Medical Oncology and Radiotherapy, KEMU/ Mayo, Hospital Rd, Lahore, wherein he has applied to act as Clinical Trial Site for phase III for clinical trial/study tilted as "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". The application is on Form-I of the Bio-Study Rules 2017 with prescribed fee of Rs. 100,000/- submitted vide slip No.76812969 dated 22nd December 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 | Rs. 100,000/- submitted vide slip No.76812969 dated 22nd December 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). | Public Sector Tertiary Care Hospital/ medical university working under Government of the Punjab.<br>Punjab Healthcare Commission **Provisional License** dated 31st May 2012 and application for issuance of regular licence dated 18th December 2021 is attached. |
| 4 | Details of premises including layout plan of the site. | Layout plan attached. |
| 5 | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | Equipment list of Emergency unit, Oncology department, Radiology Therapy and Pathology department is attached. |
| 6 | Names and qualifications of the above sections along with their staff. | Following staff list along with their CVs attached.<br>Dr. Muhammad Abbas Khokhar, Associate Professor Head of Department.<br>Dr. Nadeem Zia**, Consultant Radiotherapist,**<br>Dr. Sobia Yaub, Pharmacist,<br>Fauzia Nazir, Nurse,<br>Lehrasip Ali, DEO/ Research Coordinator. |

| | | |
|---|---|---|
| 7 | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | List of Allied Facilities, Waste Management Agreement and SOP for emergency handling attached. |
| 8 | Undertaking on stamp paper | Attached. |

3. In the light of above, it is submitted that King Edward Medical University/ Mayo Hospital, Lahore is public sector organization working under the Government of the Punjab. Mayo Hospital, Lahore is the tertiary care hospital. The applicant has applied for phase III for trial study "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".

4. .

**Decision: -**

*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.*

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**AGENDA ITEM XV:**

**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 ….*NIL*…. 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.<br>**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.<br>**List of equipment required for Bio-analytical Lab is required.** |

| | | |
|---|---|---|
| 6 | Names and qualifications of the above sections along with their staff. | List Attached.<br>**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.*

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**AGENDA ITEM XVI:**

**APPLICATION FOR APPROVAL TO ACT AS CRO AT M/S TRIAL 360 (SMC) PRIVATE LIMITED, LAHORE. (F.No.15-22/2023).**

The case is an application from Mr. Muhammad Imran Naveed, CNIC:36501-5613013-7, Director, M/s Trials 360, 140 Al-hamara Town near PCSIR, Phase II, Lahore, Punjab, Pakistan, 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 79246300059, dated 4th January 2023.

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 | Rs.300000/- submitted vide Slip number 79246300059, dated 4th January 2023. |
| 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 acknowledgment slips, Certificate of Incorporation, list of applied forms attached. |
| 4 | Details of premises including layout plan of the site. | Layout plan 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. Following are the staff working in different division of CRO.

| Name | Qualification | Division |
|---|---|---|
| Dr. Sanaullah Sajid | DVM (2011-2016)<br>, M.Phil (2016-2018)<br>, PhD (2018-2022) | Clinical Operation & Medical writing |
| DR. Samiullah Sajid | MBBS,China (2017-2023) | Medical advisor |
| Dr. Imran Naveed | Pharm D (2003-2008) | Regulatory Submission, training & Development |
| Miss Farwa Mehmood | BSc Biotecnology<br>MS Biomedical Sciences | Clinical research Associate |
| Mr. Kamran Khan | Pharm. D (2015-2020) | Project Manager |
| Dr. Shaban Afzal | MBBS, China (2017-2023) | Data Manager |
| Mr. Hafiz Bilal Murtaza | BSc, MSc (statistics)<br>M. Phil (Statistics)<br>PhD Scholar | Biostatician |
| Mrs. Aqsa Zaman | Pharm. D | Quality Assurance |
| Mr. Athar Aiman Khan | BSCS (2017-2021) | IT |
| Mr. SM Attiq Ur Rehman | B. Com (IT) | Admin & Finance |
| Mr. Ehsan Ul Haq | Applied Psychology | Admin & Finance |
| Mr. Hamza | Bachelor of Computer Science | Human Resource |

In the light of above it has been observed that only two persons are working in the organization having the degree of MBBS from china and session mentioned is 2017- 2023. Hence it is proposed that panel may be constituted by the chairman CSC as per practice or case may be placed before CSC for its

consideration. The may be requested to verify the expertise of the staff working in organization along with other requirements for CRO.

**Decision: -**
*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.*

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**AGENDA ITEM XVII:**

**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.

**Decision: -**
*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.*

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**AGENDA ITEM XVIII**

**APPLICATION FOR APPROVAL TO ACT AS CRO AT M/S CONTINUUM RESEARCH CENTER, WAH CANTT (15-20/2022 DD (PS).**

The case is an application from Miss Sanaa Anjum, CNIC:37406-1522589-8, CEO, M/s Continuum Research Center, First Floor, Anwaria Hotel Plaza, satellite Town and G.T. Road, Wah Cantt, wherein the request has been made for license to 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 40944702672, dated 18th October 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 | Page No. | Remarks |
|---|---|---|---|
| 1 | Application on prescribed Form-I of The Bio-Study Rules 2017. | 2-3 | Attached |
| 2 | Prescribed fee challan | 4 | Rs.300000/- submitted vide Slip number 40944702672, dated 18th October 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). | 12-13 | Sole Proprietor, Rental agreement attached. |
| 4 | Details of premises including layout plan of the site. | 14 | Layout plan attached. |
| 5 | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | 16 | **Firm has attached list of laboratory equipment although not applicable for CRO.** |
| 6 | Names and qualifications of the above sections along with their staff. | 17-64 | 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 | 72-73 | Attached |

3. Following are the staff working in different division of CRO.

| Name | Qualification | Division |
|---|---|---|
| Dr. Sanaa Anjum | MSc Math, M.Phil, PhD | Statistical Data Manager |

| | | |
|---|---|---|
| DR. Arfaat Yameen | B Pharm. M. Phil, PhD | Director research Evaluation and Collaboration |
| Dr. Abid Saeed Baig | B Pharm. M. Phil, PhD | Director Regulatory Affairs and Coordination. |
| Dr. Muhammad Sami | B Pharm. M. Phil, PhD | Research project Head |
| Dr. Nargis Amaan | B Pharm. M. Phil, PhD | Senior Research Analyst |
| Miss. Laiba Hasrat | B Pharm. M. Phil, | Research Analyst |
| Mr. Miss Ayesha Awan | B Pharm. M. Phil, | Research Analyst |
| Mrs. Ahmad Usman | B Pharm. M.S. | Manager Research Coordination & Management |
| Mr. Furqan Mushtaq | B. Com | Manager Accounts and Finance |
| Mr. Abubakar Noman | Msc Computer Science, MS | Data Analyst & Management / IT |

Following are the minimum division required for CRO as approved by CSC.

i. Medical Function
ii. Regulatory Submission Team
iii. Clinical Operations
iv. Data Management
v. Biostatistics
vi. Medical Writing
vii. Quality Assurance
viii. IT Team
ix. Admin & Finance
x. Human Recourse
xi. Training & Development.

It has been noticed that divisions submitted by the applicant are not as per minimum divisions approved by CSC. There is no Clinician or Physician in the team of subject CRO. All the employees are working in some other organization. They are not full time employee of the proposed CRO.

In the light of above it is proposed that following observations/ queries/ shortcomings may be communicated to the applicant.

i. Submit the Division, along with details of staff working in these division, as per divisions approved by Clinical Studies Committee.
ii. The employees working in different Divisions should be full time employee of Contract Research Organization.
iii. Government Employee should submit NOC for permission to work in other organization.
iv. MOU with City Pharmacy, Brooklyn Pharmaceuticals and Ali Pharmacy are with Wah College of Health Sciences instead of Continuum Research Organization.
v. Laboratory Equipment list attached with application. Role of this equipment in Contract Research Organization may be defined.

vi. Clinician/ physician should be the part of CRO Team.

The shortcomings have been communicated to the 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 is advised to fulfill following shortcomings/ queries:*

*i. Submit the Division, along with details of staff working in these division, as per divisions approved by Clinical Studies Committee.*

*ii. The employees working in different Divisions should be full time employee of Contract Research Organization.*

*iii. Government Employee should submit NOC for permission to work in other organization.*

*iv. MOU with City Pharmacy, Brooklyn Pharmaceuticals and Ali Pharmacy are with Wah College of Health Sciences instead of Continuum Research Organization.*

*v. Laboratory Equipment list attached with application. Role of this equipment in Contract Research Organization may be defined.*

*vi. Clinician/ physician should be the part of CRO Team.*

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**AGENDA ITEM XIX:**

**APPLICATION FOR RENEWAL OF CTU AT AGA KHAN UNIVERSITY HOSPITAL, KARACHI TO ACT AS CLINICAL TRIAL SITE FOR PHASE-I, II, III & IV CLINICAL TRIALS. F. No.15-11/2019 DD (PS)**

Application received from Dr. Saeed Sadiq Hamid (CNIC:42000-0516220-5), Director, Clinical Trial Unit, Aga Khan University Hospital, Stadium Road, Karachi, dated 07th September, 2022, received on 13th September, 2022. Wherein the request has been made for renewal of licence issued vide licence No. CTS-0003, dated 10th October, 2019, to act as CTU/CTS at Aga Khan University Hospital, Karachi. The application is on prescribed Form-III of the Bio-Study Rules 2017 with prescribed processing fee of Rs.100000/- paid vide challan No. 945048800, dated 06th September, 2022.

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

| S. No. | Required Documents / Information | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-III of the Bio-Study Rules 2017. | Attached |
| 2 | Prescribed processing fee | Rs.100000/- paid vide challan No. 945048800, dated 06th September, 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). | Attached. |
| 4 | Details of premises including layout plan of the site. | Attached. |
| 5 | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | List attached but equipment are not fulfilling requirement of |

| | | |
|---|---|---|
| | | tests required in Phase-I & Phase-II Clinical trials & the list of minimum equipment required for a bioanalytical assay in Phase-I/II Clinical Trials. Further there is no approved Bioanalytical laboratory at proposed site. Justification/reply from applicant need to be submitted. |
| 6 | Names and qualifications of the above sections along with their staff. | List of staff working at CTU, AKUH is 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. It is submitted that, the subject application was placed before the CSC in its 35th meeting, held on 13th October, 2022, for information & decision. CSC after detailed discussion & deliberations decided the case as follows: (Minutes of the meeting attached)

**Decision:**

*The CSC after detailed discussion and deliberations decided to approve the site subject to inspection panel recommendation & the Committee delegated the powers to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference.*

*Further, the Committee directed to applicant to provide details regarding Bio-Analytical Laboratories to be utilized in Phase-I & II Clinical Trial(s). In case foreign or Sponsor designated Bio-Analytical Laboratories is involved in PK/PD Assays, regulatory approval of respective country's regulatory body may be provided.*

4. Accordingly, after finalization of minutes of the meeting decision communicated vide letter bearing No. F.16-35/2022, dated 14th October, 2022.

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

i. Dr. Noor Muhammad Shah, Chairman CSC/Director, Pharmacy Services Division-DRAP.
ii. Dr. Fazal Subhan, CSC Member/ Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar.
iii. Dr. Saif Ur Rehman Khattak, In charge CDL, Karachi.
iv. Dr. Mirza Tasawer Baig, CSC Member/ Associate Professor & Clinical Pharmacist, Dr. Ziauddin Hospital, Karachi.
v. Dr. Ahson Siddiqui, CEO-Sindh Health Care Commission, Karachi.
vi. Shafqat Hussain Danish, Assistant Director (Clinical Research), Pharmacy Services Division, DRAP.

6. Accordingly, available experts panel inspected the subject site on 27th December, 2022 & submitted inspection report with following remarks:

*In compliance to letter Ref. No. F.No.15-11/2019 DD (PS) dated 20-12-2022, the nominated panel members except Dr. Noor Muhammad Shah and Dr. Saif Ur Rehman Khattak (who couldn't participate in the inspection due to their other commitments) visited the Clinical Trial Unit of Aga Khan University Hospital for verifying the facility for conduction of Phase I, II, III and IV Clinical Trials.*

*It was observed that, the site had no facility for PK/PD Bioanalytical assays. It was informed to the panel by AKUH-CTU Director that, the CTU will perform only Clinical and Pathological part of Phase I, II, III and IV Clinical Trial / Studies and the PK/PD parts will be the responsibility of the Sponsor. In the previous study of Phase-II trial, the CTU had to send assays to centralized laboratory assigned by the Sponsor.*

*Further all other required facilities, human resources, ambulatory services and emergency handling were available. However, the panel advised to expand their archiving facility and space and also storage capacity.*

*It was recommended by the panel to approve the CTU for Phase I, II, III and IV Clinical Trials except their PK/PD parts, which would be the responsibility of 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 renew the licence of M/s Aga Khan University Hospital, Karachi to act as Clinical Trial Site for Phase-I, II, III & IV Clinical Trials except their PK/PD parts, which would be the responsibility of Sponsor, under the Bio-Study Rules, 2017.*

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**AGENDA ITEM XX:**

**APPLICATION FOR LICENCE TO ACT AS CLINICAL TRIAL SITE AT PMDT-CIVIL HOSPITAL MIRPUR KHAS FOR ONGOING APPROVED endTB-Q CLINICAL TRIAL (CT#0006).**

Application Received from Dr. Abdul Bari (CNIC:42201-1013131-7), Chief Executive Officer of the Indus Hospital & Health Network, Plot C-76, Sector 31/5, Opposite Darussalam Society, Korangi Crossing, Karachi-75190, Pakistan, received on 05th April 2022. Wherein the request has been made for licensing of PMDT Site of Civil Hospital Mirpur Khas, Sindh to act as phase-III Clinical Trial Site for already approved endTB-Q Clinical Trial. The application is on prescribed Form-I of the Bio-Study Rules 2017 with prescribed processing fee of Rs.100000/- paid vide challan number 102338725, dated 24 March 2022.

2. The details of the submitted documents were as under;

| S. No. | Required Documents / Information | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-I of The Bio-Study Rules 2017. | Attached |
| 2 | Prescribed fee | Prescribed processing of Rs.100000/- paid vide challan number 102338725, dated 24 March 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 | Provincial Government Hospital. |

| | | |
|---|---|---|
| | addresses of its partners and in the case of company the name and address of the company and its directors). | |
| 4 | Details of premises including layout plan of the site. | 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 the above sections along with their staff. | Attached. |
| 7 | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | Details regarding emergency handling is not attached. |
| 8 | Undertaking on stamp paper | Attached, but not from Co-PI / responsible party of the site. |

3. After initial scrutiny following shortcomings observed:

i. Applicant should be from the site & application form & affidavit should be from responsible party/Co-PI of that site.
ii. Details regarding emergency handling need to be provided.
iii. Original fee challan (DRAP's Copy) need to be provided.
iv. IRB approval for the site along with composition need to be submitted.

4. Accordingly, after approval shortcomings letter issued on 28th April, 2022.

5. Reply in reference to this Division letter bearing even number dated 28th April 2022. received from Dr. Naseem Salahuddin (PI of endTB & endTB-Q Clinical Trials), Indus Hospital & Health Network, Plot C-76, Sector 31/5, Opposite Darussalam Society, Korangi Crossing, Karachi. Applicant submitted following requisite documents:

i. Revised application Form-I, with name of Dr. Muhammad Yaqoob, NIC number 44103-624631l-3, Chief Medical Officer and MDR TB Focal Person Clinical of PMDT site Civil Hospital Mirpurkhas, TB Unit, near Eye and ENT OPD, DHQ Civil Hospital, City Campus, Mirpurkhas - 69000, Pakistan.
ii. Affidavit on stamp paper Co-PI of subject site.
iii. Original fee challan (DRAP's Copy).

6. After re-evaluation following shortcomings were again asked to be provided:

i. Details regarding emergency handling need to be provided.
ii. IRB approval for the site along with composition need to be submitted.

7. Accordingly, after approval shortcomings letter issued on 07th July, 2022.

8. Reply in reference to this Division letter bearing even number dated 07th July, 2022 was received from Dr. Naseem Salahuddin (PI of endTB & endTB-Q Clinical Trials), Indus Hospital & Health Network, Karachi. Applicant submitted following documents:

i. Details regarding emergency handling available at PMDT Site of Civil Hospital Mirpur Khas, Sindh.
ii. NBC Amendment approval letter (Note site addition approval from NBC is not provided)
iii. IRB approval for additional site & additional/amended documents for additional site from Indus Hospital & Health Network, Karachi is attached.
iv. Other irrelevant documents, which not related to subject application are attached. (Page 39-498/Corr.)

9. After re-evaluation following shortcoming were again asked to be provided:

i. IRB approval for the site (i.e. PMDT Site of Civil Hospital Mirpur Khas, Sindh) from site IRB/ERC along with its composition need to be provided.

10. Accordingly, after approval shortcomings letter issued on 28th July, 2022.

11. Reply in reference to this Division letter bearing even number dated 28th July, 2022 was received from Dr. Naseem Salahuddin (PI of endTB & endTB-Q Clinical Trials), Indus Hospital & Health Network, Karachi. Applicant provided following required documents:

*i. IRB approval Ref: CHM/MPS/PMDT/IRB/003/2022, dated 22nd September, 2022, for PMDT Civil Hospital Mirpur Khas, Sindh.*
*ii. NBC approval for additional site (i.e. PMDT-Civil Hospital Mirpurkhas), Ref: No.4-87/NBC-410/22/94, dated 02nd August, 2022*

12. Accordingly, the Chairman CSC nominated following panel for inspection & letter bearing even number dated 01st December, 2022 issued for inspection of the site:

*i. Dr. Saif Ur Rehman Khattak, In-Charge CDL, Karachi.*
*ii. Dr. Mirza Tasawer Baig, CSC Member/ Associate Professor & Clinical Pharmacist, Dr. Ziauddin Hospital, Karachi.*
*iii. Dr. Awais Juno, Ph.D. Pharmacy Practice, Assistant Director CDL, Karachi.*

13. Accordingly, inspection conducted in compliance to this Division letter bearing even number dated 01st December, 2022. Experts panel inspected the subject site on 23rd December, 2022 & submitted inspection report with following remarks:

*Detailed observations have already been mentioned above. However, qualification and calibration record of equipment being used in the trial was not available. Furthermore, arrangements for emergency handling were also not found up to mark.*

*Keeping in view above noted observations, the site cannot be recommended without the improvement in the noted observations. Therefore, panel unanimously defers the facility for grant of clinical Trial Unit (CTU) licence.*

*Concluding status of inspection / application*

- **Deferred for improvements**

***Decision:***

*The CSC in pursuance to the recommendations of the inspection panel & in the light of discussion/deliberations decided to defer the case. Applicant is directed to submit a request when the site is ready for inspection for re-inspection.*

**AGENDA ITEM XXI:**

**APPLICATION FOR LICENSE TO ACT AS BIO ANALYTICAL LAB AT INSTITUTE OF BIOLOGICAL BIOCHEMICAL & PHARMACEUTICAL SCIENCES (IBBPS), AT DOW UNIVERSITY OF HEALTH SCIENCES, KARACHI. F. No.15-15/2019-DD (PS)**

Application was from Dr. Sadia Asim, Director, Institute of Biological, Biochemical & Pharmaceutical Sciences (IBBPS), At Dow University of Health Sciences, Karachi, dated 26th April, 2019, wherein the request has been made to license their firm with DRAP to act as a Bio Analytical Laboratory, on prescribed Form-I of the Bio-Study Rules 2017, with fee OF Rs.300000/- submitted Vide challan no. 1932881.

02. It is submitted that application evaluated according prerequisites as mentioned in Form-I of the Bio-Study Rules 2017:

| S. No. | Required Documents / Information | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-I of The Bio-Study Rules 2017. | Attached. |
| 2 | 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). | Attached. |
| 3 | Details of premises including layout plan of the site. | Attached. |
| 4 | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | Attached |
| 5 | Names and qualifications of the above sections along with their staff. | Attached |
| 6 | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | Attached |
| | Fee | Attached |
| | Undertaking | Attached |

03. Chairman CSC/Director Pharmacy Services nominated following panel for inspection of Contract Research Organization (CRO) & Bioanalytical Laboratory at M/s Institute of Biological, Biochemical & Pharmaceutical Sciences (IBBPS), At Dow University of Health Sciences, Karachi.:

| | |
|---|---|
| i. | **Dr. Abdur Rashid**<br>Chairman CSC/Director, Division of Pharmacy Services-DRAP. |
| ii. | **Prof. Dr. Nisar Hussain Shah**<br>Dean Faculty of Pharmacy,<br>Bahauddin Zakariya University, Multan |
| iii. | **Prof. Dr. Ali Jawa**<br>University of Health Sciences, Lahore. |
| iv. | **Dr. Farhana Badar**<br>Biostatistician, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore. |
| v. | **Shafqat Hussain Danish**<br>Assistant Director-DRAP. |

04. Chairman CSC/Director Pharmacy Services scheduled the inspection on 9th & 10th November 2020 & also informed that after above inspections, panel will also visit M/s Indus Hospital, Karachi, to verify progress of ongoing clinical trials at the site.

05. Due to some concerns panel revised by the then Chairman CSC.

06. Reference to discussion & informal meeting carried out in the office of Director Pharmacy Services, between Director (PS) & representatives (Dr. Sadia Asim & others) of IBBPS, Dow University of Health Sciences, Ojha Campus, Karachi on 20th June 2022.

07. Matter regarding prerequisites of Form-IIA of the Bio-Study Rules, 2017, specifically requirement of GMP & CoPP Certificate for reference product discussed in detail. Further, Dr. Sadia

Asim, Director, IBBPS, DUHS, Karachi claimed that, their application for Bio-Analytical Laboratory is still pending.

08. Director (PS)/Chairman CSC desired to forward the case details for further deliberations. Accordingly, brief regarding application is as follows:

- Application received on 26th April, 2019
- After initial evaluation shortcoming letter was issued on 04th July, 2019
- Applicant submitted reply on 09th July, 2019
- Application placed before CSC in its 5th Meeting held on 08th August 2019 and it was decided that, the inspection panel constituted for BA/BE Studies also inspect Bio-Analytical Laboratory. (Minutes attached at Page 84/Corr.)
  *"The CSC after deliberation, deferred the case & decided that the panel constituted for BA/BE Centre with also inspect the Bio Analytical Laboratory."*

- After re-evaluation & approval inspection letter issued on 26th August 2019
- Applicant submitted letter for readiness for inspection on 28th September 2020
- Applicant forwarded letter on 29th September to withdraw the letter submitted on 28th September 2020 for readiness for inspection.
- Inspection panel again constituted & letter issued on 23rd October 2020 & due to unavailability of some panel members Chairman CSC again constituted the panel & letter issued on 08th December 2020.
- Till date inspection panel haven't submitted inspection report & neither applicant submitted any application for inspection.

09. It is submitted that, the subject application was placed before the CSC in its 35th meeting held on 13th October, 2022 & the Committee decided the case as follows:

**Decision:**

*The CSC after detailed discussion and deliberation deferred the case. The Division of Pharmacy Services, will coordinate with the applicant for readiness for inspection of applied Bio-Analytical Laboratory.*

*Further, applicant is directed to submit the response within 30 days positively, after which the Chairman CSC will nominate experts for inspection as powers delegated by the Committee and if the applicant fails to reply within 30 days the application will be liable for rejection.*

10. Accordingly, CSC decision was communicated to the applicant on 14th October, 2022 & also shared through electronically.

11. Reply from Dr. Sadia Asim, Director, Institute of Biological, Biochemical & Pharmaceutical Sciences (IBBPS), At Dow University of Health Sciences, Karachi, dated 07th November, 2022, received on 16th November, 2022 & reproduced as under:

> *Respected Sir,*
> *Reference to the letter: F. No.16-35t2022 - DD (PS) dated 14th October 2022, we are pleased to inform that Bio Analytical Laboratory at Institute Biological, Biochemical & Pharmaceutical Sciences, DUHS is ready for the inspection for grant of License to act as Bio Analytical Laboratory.*
>
> *We hereby Institute Biological, Biochemical & Pharmaceutical Sciences requests the Chairman Clinical Study Committee (CSC) to nominate the panel of experts for the inspection of Bio Analytical Laboratory at Institute Biological, Biochemical & Pharmaceutical Sciences, Dow University of Health Sciences, Karachi.*

12. 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 deliberations decided to delegate its powers to the Chairman CSC for constitution of the expert panel for the inspection of proposed Bio-analytical laboratory at Institute of Biological, Biochemical & Pharmaceutical Sciences (IBBPS), Dow University of Health Sciences, Karachi.*

13. Accordingly, CSC decision was communicated on 25th November, 2022 vide letter bearing No.16-36/2022-CSC and the Chairman CSC constituted following expert panel for inspection & letter bearing even number communicated on 01st December, 2022.

i. Dr. Fazal Subhan, CSC Member/ Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar.
ii. Dr. Noor Muhammad Shah, Chairman CSC/Director Pharmacy Services Division-DRAP.
iii. Dr. Mirza Tasawer Baig, CSC Member/ Associate Professor & Clinical Pharmacist, Dr. Ziauddin Hospital, Karachi.
iv. Dr. Ahson Siddiqui, CEO-Sindh Health Care Commission, Karachi.
v. Shafqat Hussain Danish, Assistant Director (Clinical Research), Pharmacy Services Division, DRAP.

14. Accordingly, following available expert members (with prior approval from Chairman CSC & Dr. Fazal Subhan) inspected the subject site on 28th December, 2022 & submitted inspection report with following remarks:

*In compliance to letter Ref. No. F.No.15-15/2019 DD (PS) dated 10-12-2022, the nominated panel members except Prof. Dr., Fazal Subhan & Dr. Noor Muhammad Shah (who couldn't participate in the inspection due to their other commitments) visited the Bio-Analytical Lab. It was found that, the lab was equipped with required instruments, i.e. LC-MS, HPLCs, PK Study requisites.*

*The panel also visited their BA/BE Centre & CTU for proper flow during study. The panel recommended the Bio-Analytical Lab of IBBPS, DUHS.*

*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 grant licence to M/s Institute of Biological, Biochemical & Pharmaceutical Sciences (IBBPS), at Dow University of Health Sciences, Karachi to act as Bio-analytical Laboratory, Under the Bio-Study Rules, 2017.*

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**AGENDA ITEM XXII:**

**REQUEST FOR ISSUANCE OF LICENCE TO ACT AS CRO AT M/S TRUST FOR VACCINE & IMMUNIZATION, KARACHI.F. No.15-05/2022-CRO(PS)**

Application was received from Dr. Zamir Hussain Suhag (CNIC:41306-5785631-9), Director - Technical, M/s Trust for Vaccines & Immunization, situated at Suite #301, 3rd floor, Al-Sehat Centre, Adjacent to Regent Plaza Hotel, Rafiqui Shaheed Road, Karachi, dated 07th March 2022, received on 15th March 2022. Wherein the request has been made to license their firm with DRAP to act as Clinical Research Organization (CRO), the application is on prescribed Form-I of the Bio-Study Rules 2017 with prescribed processing fee of Rs.300000/-, deposited vide challan no. 55951330942, dated 09th June, 2022.

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

| S. No. | Required Documents / Information | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-I of The Bio-Study Rules 2017. | Attached |
| 2 | Fee | of Rs.300000/-, deposited vide challan no. 55951330942, dated 09th June, 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). | • FBR Certificate with NTN number 3553904-6, dated 16th May 2010.<br>• Trust Deed<br>• Certificate from Sub. Registrar under Trust Act 1882. |
| 4 | Details of premises including layout plan of the site. | Layout plan 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. | 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 stamp paper | Attached |

3. Application was placed before the CSC in its 35th meeting, held on 13th October, 2022, for information & decision. CSC after detailed discussion & deliberations decided the case as follows: (Minutes of the meeting attached)

**Decision:**

*The CSC after detailed discussion and deliberation deferred the case as inspection panel report is awaited.*

*Further, it was decided, in case of unavailability of any member the Chairman CSC will re-nominate another expert for inspection as powers delegated by the Committee.*

4. Accordingly, after finalization of minutes of the meeting decision communicated vide letter bearing No. F.16-35/2022, dated 14th October, 2022.

5. The Chairman CSC nominated following panel for inspection & letter was communicated on 07th September, 2022.

i. Dr. Ahsan Siddiqui, CEO, Sindh Health Care Commission, Karachi
ii. Dr. Awais Ahmed Juno (Ph.D. Pharmacy), Assistant Director, CDL Karachi
iii. Area FID, DRAP Karachi.

6. In compliance to this Division letter bearing even number dated 07th October, 2022. Nominated experts panel inspected the subject site on 06th December, 2022 & submitted inspection report with following remarks:

*M/s Trust for vaccines & immunization was inspected by the panel on 6th of December 2022 as per direction contained in DRAP letter No F.No.15-13/2022 DD (PS) dated 7s September 2022. The firm is non profitable organization providing medical and nutritional services to maternal and new born children across the country. They have head office at Al Sehat Center Adjacent to Regent Plaza and sub office at House C 110 Block 4, Naqsh Kazmi Road. Gulshan e lqbal, Karachi The firm has developed all the required SOPs as a Contract Research Organization which are prescribed in Bio Study Rules 2017 (attached). They have hired well experienced qualified personnel required to fulfill the criteria as sponsor contract research organization. During the inspection the panel reviewed their SOPs and other relevant documents (attached) in detail and found satisfactory. They have appointed very professional and trained qualified personal almost in every respective department to run the functions required for a CRO. Hence based on the people met, documents reviewed and facility available the panel unanimously recommended the approval of site for the purpose as referred in the afore mentioned letter.*

*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 grant licence to M/s Trust for Vaccines & Immunization, situated at Suite #301, 3rd floor, Al-Sehat Centre, Adjacent to Regent Plaza Hotel, Rafiqui Shaheed Road, Karachi, to act as Contract Research Organization, under the Bio-Study Rules, 2017.*

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**AGENDA ITEM XXIII:**

**APPLICATION FOR RENEWAL OF LICENSE NO. CTS-0015 GRANTED TO DOW UNIVERSITY OF HEALTH SCIENCES / DR RUTH KM PFAU CIVIL HOSPITAL, KARACHI. F. NO.15-32/2019 DD (PS)**

Application from Prof. Riffat Jaleel (CNIC: 42101-2253383-6), Head Unit-III, Department Gynae & Obstetrics, Dr. Ruth KM Pfau Civil Hospital Karachi, Baba e Urdu Road M.A. Jinnah Road Karachi, dated 04th August, 2022, forwarded by Prof. Rizwana Chaudhri, Head of Translational Research Department, Shifa Tameer-E-Millat University, Principal Scientist GIHD-STMU, Global Institute of Human Development Shifa Tameer-e-Millat University Director Pakistan National Coordinating Centre, Islamabad. Wherein the request has been made for renewal of Clinical Trial Site Licence No. CTS-0015, which was issued by the Division on 09th October 2019 for Department Gynae & Obstetrics & for Phase-III, Women-II Clinical Trial with approved expert staff *"Prof. Dr. Fouzia Parveen"*

02. Renewal application is on prescribed Form-III of the Bio-Study Rules 2017, along with prescribed processing fee of Rs.100000/- paid vide challan number 8614397243, dated 22nd July, 2022.

03. It is submitted that, the site was approved for Women-II Clinical Trial, which was approved for 38 months & registration letter was issued on 18th July, 2019 & trial duration will be expired on 17th September, 2022. There are only two (02) months left in trial duration & the Division haven't received application for extension in trial duration.

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

| S. No. | Required Documents / Information | Remarks |
|---|---|---|

| | | |
|---|---|---|
| i. | Application on prescribed Form-III of the Bio-Study Rules, 2017. | Attached |
| ii. | Prescribed processing fee | Rs.100000/- paid vide challan number 8614397243, dated 22nd July, 2022. |
| iii. | Phase(s) of Clinical Trial | Applied for Phase-III & IV Clinical Trials at Department of Gynae & Obstetrics.<br>Previously was approved for a Phase-III CT titled, Women-II. |
| iv. | 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). | It is informed that, applied site is a public sector, teaching, tertiary care hospital operating under Sindh Government.<br>* NOC from Hospital/Department head on their letter head, need to be submitted for utilization of Unit-II & III or any other ward/unit as a CTS for Women-II Clinical Trial need to be provided. |
| v. | Details of premises including layout plan of the site. | Layout plan of applied site/department is not provided. |
| vi. | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | Not provided. |
| vii. | Names and qualifications of the above sections along with their staff. | Names and qualifications of staff working at Gynae Ward Unit-II & Unit III are attached. |
| viii. | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | Attached. |
| ix. | Undertaking on stamp paper | Copy of affidavit attached, original need to be provided. |

05. In view of para 21-22/N, following shortcomings observed after initial scrutiny:

i. The licence CTS No 00015 was granted and approved for expert Prof. Dr. Fouzia Parveen for a Phase-III Clinical Trial (i.e. Women-II) only. Clarification/reason for change of Co-PI in renewal application is required.
ii. NOC from Hospital/Department head on their letter head, need to be submitted for utilization of Unit-II & Unit-III or other units of Department of Gynae & Obstetrics, Dr. Ruth KM Pfau Civil Hospital Karachi as a CTS for Women-II Clinical Trial need to be provided.
iii. Layout plan of applied site/department is not provided.
iv. Details of the section wise equipment and machinery available at Department of Gynae & Obstetrics, Dr. Ruth KM Pfau Civil Hospital Karachi, which will be utilized in the trial needs to be provided.
v. Renewal application is for Phase-III & IV Clinical Trials at Department of Gynae & Obstetrics, Whereas, previously issued licence (i.e. CTS-0015) was approved for a Phase-III CT titled, Women-II only.
vi. There are two different IRB approval addressing Prof. Riffat Jaleel for Unit-I & Prof Dr. Sarah Kazi for Unit-III, Department Gynae & Obstetrics, Dr. Ruth KM Pfau Civil Hospital Karachi with same date of issuance are attached. Clarification regarding PI of the site & IRB approval(s) need to be submitted. Whereas renewal application is from Prof. Riffat Jaleel for Unit-II & III, Department of Gynae & Obstetrics, Dr. Ruth KM Pfau Civil Hospital Karachi.
vii. Copy of affidavit attached, original need to be provided.

06. Accordingly, shortcomings were shared on 31st August, 2022.

07. Reply from Prof. Dr. Rizwana Chaudhri (National PI of Women-II CT), Head of Translational Research Department, Shifa Tameer-E-Millat University, Principal Scientist GIHD-STMU, Global Institute of Human Development Shifa Tameer-e-Millat University Director Pakistan National Coordinating Centre, Islamabad. Wherein the reply is in reference to this Division's letter even number dated 10th August, 2022, by which shortcomings of licence renewal application were communicated to the applicant.

08. Submitted reply along with attachments is as follows:

| Sr. | Descriptions | Reply | Remarks |
|---|---|---|---|
| i. | The License CTS No 0015 granted and approved for expert, Prof Dr. Fouzia Perveen for a Phase III clinical trial (i.e. Woman II) only. Clarification/reason for change of Co-PI in renewal application is required. | The license was granted to Prof Fouzia Perveen as she was the Head of Department (HOD) of Obstetrics/Gynae at Civil Hospital Karachi at that time, so the application was from her side. Since Civil Hospital Karachi is a government hospital and abides by rules and regulations of government service structure, hence Prof Fouzia Perveen retired and now Prof Riffat Jaleel has taken over as the HOD of Obstetrics/Gynae at Civil Hospital Karachi. Hence the current application of renewal of license is from Prof Riffat Jaleel. | --- |
| ii. | NOC from Hospital/Department head on his/her letterhead, need to be submitted for utilization of Unit II and Unit III or other units of Department of Gynae/Obstetrics, DR RUTH KM PFAU Civil Hospital Karachi as a CTS for WOMAN 2 clinical trial. | Please find attached the requested NOC herewith in **Appendix I.** | --- |
| iii. | Layout plan of applied site/department needs to be submitted. | Please find attached the layout plan of Department of Gynae/Obstetrics of DR RUTH KM PFAU Civil Hospital Karachi in **Appendix II.** | --- |
| iv. | Details of the section wise equipment and machinery available at Department of Gynae / Obstetrics of DR RUTH KM PFAU Civil Hospital Karachi, which will be utilized in the trial needs to be provided. | Please find attached the revised application in **Appendix III**, requested changes have been made in details of the section wise equipment and machinery available at the site, which will be utilized in Women II clinical trial & Gynae related Phase III & IV Clinical trials. | --- |
| v. | Renewal application is for Phase III & IV clinical trials at Department of Gynae/Obstetrics, whereas, previously issued license (i.e. CTS-0015) was approved for a Phase III CT titled Woman II only. | The original application for the site registration of DR RUTH KM PFAU Civil Hospital Karachi, was for both Phase III and IV trials, however the DRAP approval, only mentioned phase III trial, taking into consideration that Woman Two was phase III trial. Our sites registration applications were among the few earliest applications prepared by our center; therefore, some short coming | --- |

| | | | |
|---|---|---|---|
| | | might be intrinsic to them. We therefore request DRAP to consider our apology for any miscommunication from our part and consider our site for both phase III and IV trials as per Bio-Study rule 2017. Dr. Ruth Km Pfau Civil Hospital Karachi is a renowned tertiary care hospital in public sector, providing state of art Obstetrical and Gynecological care and therefore adequately equipped in term human and material resources for conduction of phase III and IV related trials, We would be immensely grateful if DRAP considers registration of Dr. Ruth Km Pfau Civil Hospital Karachi, for both phase III and IV trial. | |
| vi. | Application is from Prof Riffat Jaleel for Unit II & III whereas, two different IRB approvals for Unit II & UNIT III addressing Prof Riffat Jaleel & Prof Dr. Sarah Kazi with same date of issuance are attached, clarification required. | It was a typing mistake in the application submitted; please accept our apology for it. We have applied for renewal of license at Unit I and Unit III. Prof Riffat Jaleel is the HOD of Obstetrics/Gynae at Civil Hospital Karachi and the Principal Investigator (Pl) at Unit III, while Prof. Sarah Kazi is the Co-Pl at Unit I Please find attached the revised application in Appendix III, requested changes have been made in the number of units. | --- |
| vii. | Copy of Affidavit attached original need to be provided | Original Affidavit as provided by the institution was already attached with the application. Please find attached the copy of submitted Affidavit for your reference in **Appendix IV.** | Only a color copy of affidavit I again provided, original affidavit still need to be provided. |
| viii. | It is intimated that, the site was approved for Woman II clinical trial for 38 months & registration letter was issued on 18th July,2019 & trial duration will expire on 17th September, 2022.There are only two months left in trial duration & the Division haven't received application for extension in trial duration. | An application for extension of Woman Two trial till 12th of May, 2023, was submitted to the Drug Regulatory Authority of Pakistan on 7th September,202L along with processing fee of Rs 25,000. DRAP response to our application was received on 2nd November, 2021, (Reference No. F.No.03/03-2019 DD (PS)), detailing the shortcomings in our application. The response to the above letter was submitted on 2gth November, 2021. The approval of trial extension from local ethics committees of all the participating trial sites were obtained and submitted to DRAP on 23'd May,2022. DRAP receipts of the protocol extension application, response to the query raised and submission of Local Ethics Approvals, are attached for your reference in **Appendix V.** | |

09. Accordingly, again shortcoming letter issued on 01st December, 2022.

10. The Chairman CSC nominated following panel for inspection.

i. Dr. Fazal Subhan, CSC Member/ Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar.
ii. Dr. Saif Ur Rehman Khattak, Incharge CDL, Karachi.
iii. Dr. Mirza Tasawer Baig, CSC Member/ Associate Professor & Clinical Pharmacist, Dr. Ziauddin Hospital, Karachi.
iv. Dr. Ahson Siddiqui, CEO-Sindh Health Care Commission, Karachi.
v. Shafqat Hussain Danish, Assistant Director (Clinical Research), Pharmacy Services Division, DRAP.

11. Nominated panel members (with prior verbal approval from Chairman CSC) inspected the subject site on 30th December, 2022 & submitted inspection report with following remarks:

*In compliance to letter Ref. No. F.No.15-32/2019 DD (PS) dated 20-12-2022, the nominated panel members except Prof. Dr., Fazal Subhan & Dr. Saif Ur Rehman Khattak (who couldn't participate in the inspection due to their other commitments) visited the Clinical Trial Site of Department of Gynae and Obstetrics for Women-2 Trial Study.*
*It was observed that, the site need improvement in IMP Storage and Data Archiving Facility. Furthermore, it was found that, the Pharmacist was not in the study/trial rather as employee of the Hospital and wasn't involve in dispensing.*
*The panel was in the opinion that; the site has been conducting the same trial and recommended for renewal.*
*However, the recommendations of involving Pharmacist for IMP storage and dispensing and expansion of storage and archiving facility is also submitted*

*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 renew the licence of M/s Dr. Ruth KM Pfau Civil Hospital Karachi, Baba e Urdu Road M.A. Jinnah Road Karachi, to act as Clinical Trial Site at Unit-II & Unit-III Gynae & Obstetrics Department for Phase-III & Phase-IV Gynae & Obstetrics related trials only, under the Bio-Study Rules, 2017.*

*Further, National PI & Site-PI are advised to appoint & involve Pharmacist for IMP storage, dispensing and expand storage and archiving facility at the site & submit compliance report for issuance of renewal.*

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**AGENDA ITEM XXIV:**

**APPLICATION FOR RENEWAL OF LICENSE NO. CTS-0016 GRANTED TO JINNAH POSTGRADUATE MEDICAL CENTRE, KARACHI, F. No.15-33/2019 DD (PS)**

Application received from Prof. Haleema Yasmin (CNIC:42307-9061604-4) & Dr. Saba Khan (CNIC:35200-1062237-0), professors of Gynae Ward-08 & Ward-09 respectively, Jinnah Post Graduate Medical Centre, Rafiqui Shaheed Road, Karachi., dated 15th July, 2022, forwarded by Prof. Rizwana Chaudhri, Head of Translational Research Department, Shifa Tameer-E-Millat University, Principal Scientist GIHD-STMU, Global Institute of Human Development Shifa Tameer-e-Millat University Director Pakistan National Coordinating Centre, Islamabad. Wherein the request has been

made for renewal of Clinical Trial Site Licence No. CTS-0016, which was issued by the Division on 09th October 2019 for Gynae Ward-09 & for Phase-III, Women-II Clinical Trial (Page 20/Corr.)

02. Renewal application is on prescribed Form-III of the Bio-Study Rules 2017, along with prescribed processing fee of Rs.100000/- paid vide challan number 852209044, dated 27th June, 2022.

03. It is submitted that, the site was approved for Women-II Clinical Trial, which was approved for 38 months & registration letter was issued on 18th July, 2019 & trial duration will be expired on 17th September, 2022. There are only two (02) months left in trial duration & the Division haven't received application for extension in trial duration.

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

| S. No. | Required Documents / Information | Remarks |
|---|---|---|
| i. | Application on prescribed Form-III of the Bio-Study Rules, 2017. | Attached |
| ii. | Prescribed processing fee | Rs.100000/- paid vide challan number 852209044, dated 27th June, 2022. |
| iii. | Phase(s) of Clinical Trial | Applied for Phase-III & IV Clinical Trials related to Gynae & Obstetrics. |
| iv. | 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). | It is informed that, applied site is a provincial government hospital operating under Sindh Government.<br>* NOC from Hospital/Department head on their letter head, need to be submitted for utilization of Ward-08 & Ward-09 as a CTS for Women-II Clinical Trial need to be provided. |
| v. | Details of premises including layout plan of the site. | Details of premises regarding Gynae Ward-08 & 09 along with layout plan need to be provided. |
| vi. | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | Not provided. |
| vii. | Names and qualifications of the above sections along with their staff. | Names and qualifications of staff working at Gynae Ward-08 & Ward-09 are attached. |
| viii. | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | Attached but need to provide details regarding emergency handling facilities available at Gynae Ward-08 & 09 of JPMC. |
| ix. | Undertaking on stamp paper | Attached. |

05. In view of para 28-29/N, following shortcomings observed after initial scrutiny:

i. NOC from Hospital/Department head on their letter head, need to be submitted for utilization of Ward-08 & Ward-09 as a CTS for Women-II Clinical Trial need to be provided.
ii. Details of premises regarding Gynae Ward-08 & 09 along with layout plan need to be provided.
iii. Details of the section wise equipment and machinery available at Gynae Ward-08 & 09 & which will be utilized in the trial need to be provided.
iv. Details of the allied facilities need to provide regarding emergency handling & ambulatory services/facilities available at Gynae Ward-08 & 09 of JPMC.
v. Attached IRB approval can't be considered as composition of IRB is not as per ICH-GCP Guidelines & the Bio-Study Rules, 2017. Further, there is also Conflict of Interest as PI is also part of IRB. It is

therefore advised re-notify IRB/ERC of JPMC as per ICH-GCP Guidelines & the Bio-Study Rules, 2017 & get a fresh approval from re-notified IRB & NBC.

06. Accordingly, shortcomings were shared on 10th August, 2022.

07. Reply received from Prof. Haleema Yasmin (CNIC:42307-9061604-4), Professors & Head of Gynae Ward-08 & Ward-09, Jinnah Post Graduate Medical Centre, Rafiqui Shaheed Road, Karachi., dated 14th September, 2022. Applicant in reference to this Division's letter even number dated 10th August, 2022, provided following documents:

*i. Revised application form (Form-III of the Bio-Study Rules, 2017)*
*ii. NOC from Prof Shahid Rasul, Executive Director, Jinnah Post Graduate Medical Centre Karachi.*

08. Reply also received from Prof. Rizwana Chaudhri (National PI of Women-II Clinical Trial), Head of Translational Research Department, Shifa Tameer-E-Millat University, Principal Scientist GIHD-STMU, Global Institute of Human Development Shifa Tameer-e-Millat University Director Pakistan National Coordinating Centre, Islamabad. Wherein reply is in reference to this Division's letter even number dated 10th August, 2022.

09. Submitted reply along with attachments is as follows:

| Sr. | Descriptions | Reply | Remarks |
|---|---|---|---|
| i. | The license CTS No 0015 was granted and approved for expert Dr. Khadija Bano for Gynae ward 09 of JPMC for phase III only. As the Gynae ward No 08 of JPMC was not licensed so its renewal on form III can't be considered. Clarification/reason for change of Co-Pl and addition of Gynae ward 08 in renewal application is required. Details with declaration /undertaking that no change has been made be provided for the premises along with layout of Gynae ward 09 of JPMC if you intend to proceed for renewal of already issued CTS license referred above otherwise application for a new license should be submitted if it is required for both the wards. | The license was granted to Prof Khadija Bano as she was the Head of Department (HOD) of Obstetrics / Gynae and principal Investigator (Pl) of ward 09 at JPMC at that time, so the application was from her side and ward 09 was mentioned as a part of designation of Prof Khadija Bano; but Prof Khadija Bano as a HOD, included the details of both wards 08 and ward 09 in the original application submitted for approval. Since JPMC is a government hospital and abides by rules and regulations of government service structure, hence prof Khadija Bano retired and now Prof Haleema Yasmin has taken over as the HOD of Obstetrics/Gynae at JPMC. Hence the current application of renewal of license is from Prof Haleema Yasmin and she has applied for the renewal of registration of both units at JPMC. Dr. Saba Khan has taken over as the Pl of ward 09 after the retirement of Prof Khadija Bano. Both the wards 08 and 09 share the same premises and utilize the same material resources for providing tertiary care facilities to the women. Please find attached undertaking from Prof Haleema Yasmin confirming that no change has been made to the premises of both wards at JPMC in Appendix l. Our sites' registration applications were among the few earliest applications prepared by our center; therefore, some short coming might be intrinsic to them. We therefore request DRAP to consider our apology for any miscommunication from our part and consider both units in your renewal approval. We will be really grateful. | --- |
| ii. | Details of the section wise equipment and machinery available at Gynae ward 09 & which will be utilized in the trial need to be provided. | Please find attached the revised application in Appendix II, requested changes have been made in details of the section wise equipment and machinery available at the site, which will be utilized in the trial. | --- |
| iii. | Details of the allied facilities need to provide regarding emergency handling & ambulatory | Please find attached the revised application in Appendix II, requested changes have been made in details regarding emergency handling & | --- |

| | | | |
|---|---|---|---|
| | services/facilities available at Gynae ward 09 of JPMC . | ambulatory services/facilities available at JPMC. | |
| iv. | NOC from Head of Institution/Hospital on letter head, need to be submitted for utilization of Gynae wards as a CTS for Women II clinical trial, needs to be provided. | Please find attached the requested NOC herewith. | --- |
| v. | It is intimated that, the site was approved for Woman II clinical trial for 38 months & registration letter was issued on 18th July,2019 & trial duration will be expired on 17th September, 2022.There are only two months left in trial duration & the Division haven't received application for extension in trial duration. | An application for extension of Woman Two trial till 12th of May, 2023, was submitted to the Drug Regulatory Authority of Pakistan on 7th September,2021, along with processing fee of Rs 25,000. DRAP response to our application was received on 2nd November, 2021, (Reference No. F.No.03/03-2019 DD (PS)), detailing the shortcomings in our application. The response to the above letter was submitted on 29th November, 2021. The approval of trial extension from local ethics committees of all the participating trial sites were obtained and submitted to DRAP on 23rd May,2022, DRAP receipts of the protocol extension application, response to the query raised and submission of Local Ethics Approvals, are attached for your reference. | --- |

10. The Chairman CSC nominated following panel for inspection.

i. Dr. Fazal Subhan, CSC Member/ Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar.
ii. Dr. Saif Ur Rehman Khattak, In-Charge CDL, Karachi.
iii. Dr. Mirza Tasawer Baig, CSC Member/ Associate Professor & Clinical Pharmacist, Dr. Ziauddin Hospital, Karachi.
iv. Dr. Ahson Siddiqui, CEO-Sindh Health Care Commission, Karachi.
v. Shafqat Hussain Danish, Assistant Director (Clinical Research), Pharmacy Services Division, DRAP.

11. Nominated panel members (with prior verbal approval from Chairman CSC) inspected the subject site on 29th December, 2022 & submitted inspection report with following remarks:

*In compliance to letter Ref. No. F.No.15-33/2019 DD (PS) dated 20-12-2022, the nominated panel members except Prof. Dr., Fazal Subhan & Dr. Saif Ur Rehman Khattak (who couldn't participate in the inspection due to their other commitments) visited the Clinical Trial Site of JPMC, located at Ward 8 and 9 in Department of Obstetrics and Gynae, to review & verify the facility for Women-2 Trial.*

*It was observed that, the site was lacking Pharmacist and the storage area of site was also not well equipped. They were also informed to expand their storage and archiving area. The panel was of the opinion that; the site has already given approval for Women-2 Trial and for that they have the capacity to conduct the trial.*

*Therefore, their renewal was recommended with the recommendation of having a Pharmacist in the trial and the mentioned observation.*

*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 renew licence of M/s* Jinnah Post Graduate Medical Centre, Rafiqui Shaheed Road, Karachi, *to act as Clinical Trial Site at Gynae Ward-08 & 09 for Phase-III & Phase-IV Gynae & Obstetrics related trials only, under the Bio-Study Rules, 2017.*

*Further, National PI & Site-PI are advised to appoint & involve Pharmacist for IMP storage, dispensing and expand storage and archiving facility at the site & submit compliance report for issuance of renewal.*

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**AGENDA ITEM XXV:**

**APPLICATION FOR RENEWAL OF LICENSE NO. CTS-0011, GRANTED TO CLINICAL TRIAL SITE, AT SHAIKH ZAID WOMEN HOSPITAL, CHANDKA MEDICAL COLLEGE, SHAHHED BENAZIR BHUTTO MEDICAL UNIVERSITY, LARKANA. F. No.15-26/2019 DD (PS)**

Application is from Prof. Dr. Shahida Shaikh (CNIC:42201-3827757-0), Department of Obstetrics /Gynae, Sheikh Zayed Women Hospital, Chandka Medical College, Shaheed Mohtarma Benazir Bhutto Medical University Larkana, dated 15th July, 2022, forwarded by Prof. Rizwana Chaudhri, Head of Translational Research Department, Shifa Tameer-E-Millat University, Principal Scientist GIHD-STMU, Global Institute of Human Development Shifa Tameer-e-Millat University Director Pakistan National Coordinating Centre, Islamabad. Wherein the request has been made for renewal of Clinical Trial Site Licence No. CTS-0011, which was issued by the Division on 09th October 2019 for Department of Gynae & Obs, Shaikh Zaid Women Hospital, Chandka Medical College, Shaheed Benazir Bhutto Medical University, Larkana, for Phase-III, Women-II Clinical Trial (Page 12/Corr.)

02. Renewal application is on prescribed Form-III of the Bio-Study Rules 2017, along with prescribed processing fee of Rs.100000/- paid vide challan number 8604823491, dated 27th June, 2022.

03. It is submitted that, the site was approved for Women-II Clinical Trial, which was approved for 38 months & registration letter was issued on 18th July, 2019 & trial duration will be expired on 17th September, 2022. There are only two (02) months left in trial duration & the Division haven't received application for extension in trial duration.

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

| S. No. | Required Documents / Information | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-III of the Bio-Study Rules, 2017. | Attached |
| 2 | Prescribed processing fee | Rs.100000/- paid vide challan number 8604823491, dated 27th June, 2022. |
| 3 | Phase(s) of Clinical Trial | Applied for Phase-III & IV Clinical Trials related to Gynae & Obstetrics. |
| 4 | 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). | It is informed that, it's a tertiary care Hospital established in 1974. It deals with obstetrics and gynecology with total 3 units consisted of 200 hundred beds. It is affiliated with Chandka Medical College, Shaheed Mohtarma Benazir Bhutto Medical University, Larkana. Here we have outpatient department emergency department for Obstetrics & Gynecology only operation theater and labor room.<br>* NOC from Hospital/Department head is attached. |
| 5 | Details of premises including layout plan of the site. | Attached. |
| 6 | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | Attached. |

| | | |
|---|---|---|
| 7 | Names and qualifications of the above sections along with their staff. | Names and qualifications of staff working at Department of Gynae/Obs, SZWH, Larkana are attached. |
| 8 | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | Attached. |
| 9 | Undertaking on stamp paper | Attached. |

05. The Chairman CSC constituted following inspection panel for verification of facilities at proposed site which are required for Phase-III & IV Gynecology related Clinical Trials.

i. Dr. Noor Muhammad Shah, Chairman CSC/Director, Division of Pharmacy Services-DRAP.
ii. Dr. Ahson Siddiqui, CEO, Sindh Health Care Commission, Karachi.
iii. Dr. Aamir Jaffrey, Sindh Institute of Urology & Transplantation, Karachi.
iv. Dr. Saif Ur Rehman Khattak, Director/Incharge, Central Drug Laboratory, Karachi.
v. Dr. Awais Ahmad June, Ph.D. (Pharmacy Practice), Assistant Director CDL-Karachi.

06. Following available expert members inspected the subject site on 25th January, 2023 & submitted inspection report with following remarks:

*i. Dr. Saif Ur Rehman Khattak, Incharge CDL, Karachi.*
*ii. Dr. Ahson Siddiqui, CEO-Sindh Health Care Commission, Karachi.*
*iii. Dr. Awais Juno, Assistant Director-CDL Karachi.*

**Remarks:**

*With reference to inspection letter Ref. No. F.No.15-26/2019 DD (PS) dated 16th December, 2022, following members visited the Clinical Trial Site, situated at Department of Obstetrics/Gynae, Sheikh Zayed Women Hospital, Chandka Medical College, Shaheed Mohtarma Benazir Bhutto Medical University Larkana on 25-01-2023.*

*During inspection all relevant requirements were checked as per above checklist and found satisfactory and up to the mark. GCP & Pharmacovigilance training record of staff was available. Dr. Aamir Jaffary and Dr. Noor Muhammad Shah could not join the inspection due to*
*Keeping in view, above panel unanimously recommend the renewal of Clinical Trial Site for Phase-III & Phase-IV Gynae related Clinical Trials, specially for Clinical Trial titled, Tranexamic Acid (TXA) for reducing Postpartum Bleeding in Women with Anemia: An International Randomized, Double Blind, Placebo Controlled Trial (Women-II Trial).*

*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 decided to renew the licence of M/s Sheikh Zayed Women Hospital, Chandka Medical College, Shaheed Mohtarma Benazir Bhutto Medical University Larkana, to act as Clinical Trial Site at Department of Obstetrics /Gynae for Phase-III & Phase-IV Gynae & Obstetrics related trials only, under the Bio-Study Rules, 2017.*

*Further, National PI & Site-PI are advised to appoint & involve Pharmacist for IMP storage, dispensing and expand storage and archiving facility at the site & submit compliance report for issuance of renewal.*

**AGENDA ITEM XXVI:**

**APPLICATION FOR RENEWAL OF LICENCE NO. CRO-0003, TO ACT AS CONTRACT RESEARCH ORGANIZATION FROM M/S METRICS RESEARCH (PVT) LTD., KARACHI. F. No.15-21/2022-CRO.**

Application from Dr. Murtaza Hussain (CNIC: 42401-1851267-5), Chairman/CEO, M/s Metrics Research (Pvt) Ltd, Plot No. B-10, Block 16, WCHS, KDA scheme No.24, Gulshan-e-Iqbal, Karachi – Pakistan. Wherein the request has been made for renewal of license No. CRO-0003 to continue to work as Clinical Research Organization (CRO), under the Bio-Study Rules, 2017. The application is on prescribed Form-III of the Bio-Study Rules, 2017 & prescribed processing fee of Rs. 300,000/- deposited vide challan no. 754173158474, dated 09th December, 2022.

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2. Further, the CRO also informed that, they have also relocated their office on the address mentioned below & the address also updated in the tax certificate, Form-21 & Form-A (under the Companies Act, 2017) & submitted a request to kindly update the office location/address in the DRAP records for future correspondence & inspection, please.

- *B-10, Block 16, WCHS, KDA scheme No.24, Gulshan-e-Iqbal, Karachi – Pakistan.*

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

| S. No. | Required Documents / Information | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-I of The Bio-Study Rules 2017. | Attached |
| 2 | Prescribed processing fee | Rs. 300,000/- deposited vide challan no. 754173158474, dated 09th December, 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). | • FBR Certificate with NTN number 2998398, dated 16th November, 2022.<br>• Form-21, Form-A (under the Companies Act, 2017)<br>• List of Directors |
| 4 | Details of premises including layout plan of the site. | 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. | List of division wise employees along with their CVs is 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 stamp paper | Attached. |

**Decision:**

*The CSC delegated the power to the Chairman CSC for constitution of the inspection panel to visit the site for verification/confirmation of required facilities available at CRO. Nominated panel after inspection will generate a report which will be placed before the CSC for consideration.*

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**AGENDA ITEM XXVII:**

**APPLICATION TO REGISTER THE AGA KHAN HOSPITAL FOR WOMEN & CHILDREN, KHARADAR, KARACHI AS STUDY SITES FOR A PHASE-II CLINICAL TRIAL TITLED, "CAN ESOMEPRAZOLE IMPROVE OUTCOMES IN WOMEN AT HIGH RISK OF PRE-ECLAMPSIA, A PHASE-II, PLACEBO-CONTROLLED RANDOMIZED MULTICENTER CLINICAL TRIAL (THE ESPRESSO STUDY)". F. No.15-16/2022 DD (PS)**

Application was from Dr. Syed Mairajuddin Shah, Chief Operating Officer (COO), Secondary Hospital, Aga Khan University Hospital, Stadium Road, Karachi, dated 15th August 2022. Wherein the request has been made to license the subject site for Phase-II Clinical Trial titled, "Can Esomeprazole Improve Outcomes in Women at High Risk of Pre-Eclampsia, a Phase-II, Placebo-Controlled Randomized Multicenter Clinical Trial (The Espresso Study), the application is on prescribed Form-I of the Bio-Study Rules, 2017 with prescribed processing fee of Rs.100000/- paid vide challan No. 23729484194, dated 03rd August, 2022.

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

| S. No. | Required Documents / Information | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-I of The Bio-Study Rules 2017. | Attached |
| 2 | Fee | Prescribed processing fee of Rs.100000/- is paid vide challan No. 23729484194, dated 03rd August, 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). | Attached. |
| 4 | Details of premises including layout plan of the site. | Attached. |
| 5 | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | Some details are provided but equipment & facilities are not fulfilling requirement of tests required in Phase-II Clinical trials & the list of minimum equipments required for a bioanalytical assay in Phase-I/II Clinical Trials. Further there is no approved Bioanalytical laboratory at proposed site. |
| 6 | Names and qualifications of the above sections along with their staff. | Attached. |

| | | |
|---|---|---|
| 7 | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | Some of details are provided but the facilities available at the proposed primary Health care Site are not enough to conduct a Phase-II Clinical Trial at the site. |
| 8 | Undertaking on stamp paper | Attached. |

3. After initial scrutiny following shortcomings observed:

i. List of section wise equipment and machinery required for analytical or bio-analytical and clinical studies is not provided.
ii. Equipments mentioned in the list are not fulfilling requirement of tests/assay required in Phase-II Clinical Trials (i.e. Pharmacokinetic & Pharmacodynamics Studies).
iii. Further there is no approved Bioanalytical laboratory at proposed trial site, which is required for Phase-I/ Phase-II Clinical Trials.
iv. Allied facilities & emergency handling facilities available at the proposed Primary Health Care Site are not enough to conduct a Phase-II Clinical Trial at the site.
v. Approval from Health Care Commission of Sindh need to be provided.

4. It is submitted that, the case was placed before CSC in its 35th meeting held on 13th October, 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 shortcomings as per Form-II of the Bio-Study Rules, 2017:*

*i. List of section wise equipment and machinery required for analytical or bio-analytical and clinical studies is not provided.*
*ii. Equipments mentioned in the list are not fulfilling requirement of tests/assay required in Phase-II Clinical Trials (i.e. Pharmacokinetic & Pharmacodynamics Studies).*
*iii. Further there is no approved Bioanalytical laboratory at proposed trial site, which is required for Phase-I/ Phase-II Clinical Trials.*
*iv. Allied facilities & emergency handling facilities available at the proposed Primary Health Care Site are not enough to conduct a Phase-II Clinical Trial at the site.*
*v. Approval from Health Care Commission of Sindh need to be provided.*

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

5. Accordingly, CSC decision communicated to applicant on 14th October, 2022, but yet response is awaited.

6. It is submitted that, the case was placed before CSC in its 36th 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 shortcomings as per Form-II of the Bio-Study Rules, 2017:*

*i. List of section wise equipment and machinery required for analytical or bio-analytical and clinical studies is not provided.*
*ii. Equipments mentioned in the list are not fulfilling requirement of tests/assay required in Phase-II Clinical Trials (i.e. Pharmacokinetic & Pharmacodynamics Studies).*
*iii. Further there is no approved Bioanalytical laboratory at proposed trial site, which is required for Phase-I/ Phase-II Clinical Trials.*

iv. *Allied facilities & emergency handling facilities available at the proposed Primary Health Care Site are not enough to conduct a Phase-II Clinical Trial at the site.*
v. *Approval from Health Care Commission of Sindh need to be provided.*

*Further, applicant was given one last opportunity to provide requisite documents within 15 days positively, failing which the application will be liable to be rejected.*

7. CSC decision was communicated vide letter bearing number F.No.16-36/2022-CSC dated 25th November, 2022.

8. Reply from Dr. Syed Mairajuddin Shah, Chief Operating Officer (COO), Secondary Hospital, Aga Khan University Hospital, Stadium Road, Karachi received on dated 09th December, 2022, in reference to this Division letter bearing even number dated 25th November, 2022.

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

*Shortcoming-I: List of section wise equipment and machinery required for analytical or bio-analytical and clinical studies is not provided.*
**Response:** Although, we don't require any analytical or bioanalytical testing/ procedures for this phase II Trial ESPRESSO, the following sections/ departments will be involved:

- Gynecology and Obstetrics Clinics (for enrollment purpose)
- Inpatient services - Hospital Admissions
- Clinical Lab (for collecting and archiving biological samples)
- Ultrasound Department
- Pre-Labor room
- Labor room
- Urgent care services in case of any emergency
- Pharmacy (For investigational product storage and inventory)
- Operating room (in case of cesarean section or any other gynecological surgeries)
- Day care surgeries

*Shortcoming-II: Equipments mentioned in the list are not fulfilling requirement of tests/assay required in Phase-II Clinical Trials (i.e. Pharmacokinetic & Pharmacodynamics Studies).*

**Response:** For ESPRESSO, there is no need to carry out any bioanalytical tests on site, rather; all the biological samples will be shipped to the sponsor that is the University of Sydney and there the analysis will take place. For this purpose, a Material Transfer Agreement (MTA) is in place and attached. The investigational product is well marketed and is being used routinely in pregnant women; however, the indication has been changed.

*Shortcoming-III: Further there is no approved Bioanalytical laboratory at proposed trial site, which is required for Phase-I/ Phase-II Clinical Trials.*

**Response:** As mentioned above, for ESPRESSO, there is no need to carry out any bioanalytical tests on site, rather; all the biological samples will be shipped to the sponsor that is the University of Sydney and there the analysis will take place. For this purpose, a Material Transfer Agreement (MTA) is in place and attached.

*Shortcoming-IV: Allied facilities & emergency handling facilities available at the proposed Primary Health Care Site are not enough to conduct a Phase-II Clinical Trial at the site.*

**Response:** The Aga Khan Hospital for Women and Children, Kharadar (AKHW&C) is a secondary health care unit affiliated with the Aga Khan university Hospital. It has two campuses across from each other separated by a single road: (i) Hospital Building where the general patient wards, private rooms, operating rooms, diagnostics, and pharmacy can be found (inpatients) (ii) The Aga Khan Diagnostic Centre where the clinics, laboratory, and diagnostics for visiting patients (outpatients) is located. The team consists of highly qualified, trained, and experienced doctors, nurses, technicians and administrative staff that are available to provide compassionate care, diagnosis and treatment for expecting mothers, manage labour and delivery, as well as deal with women's health and children's health issues and (inpatients) provide emergency services.

Sub-specialty services available at the Aga Khan Hospital for Women & Children, Kharadar include consulting clinics for neonates, women and children, anesthesia, radiology, laboratory, and physiotherapy; in addition to an ln-patient facility for women, children, and neonates.

Urgent Care Services (UCS) is also a significant part of the services provided at Kharadar secondary hospital. UCS operates from 1000 to 1800 hours, catering urgent care and as an outpatient treatment. A registered midwife is assigned in the UCS and on duty doctors give coverage as per the need. After 1800 hours' services will be provided via inpatient units. Patient assessed by assigned nursing staff and doctor. After assessing the patient, the required investigation and treatment is carried out. The scope of services and clinic schedule is attached for your ready reference.

Since Kharadar site is equipped with trained health care staff and has a facility of dealing with emergency cases round the clock, this site is appropriate for this phase II Trial in our understanding. Further, if a patient needs to be referred, there is a proper in-built mechanism of referral. Usually the patients requiring advanced care are transferred to main AKU which is a tertiary care hospital with 2417 urgent and specialized care services to ensure a high standard of quality care. AKU's Emergency Department is a 62-bed facility
that provide emergency services to an average of 170 patients daily and more than 60,000 patients every year. It includes:

- 4-bed Resuscitation Room,
- 4-bed Resuscitation Step Down Room with 2 ventilators (breathing machines),
- 16-bed Critical Care Area,
- 12-bed Observation Area,
- 8 Clinical Decision Units,
- 10-bed dedicated child (pediatric) Area,
- 1 Isolation Room,
- 1 Emergency Room,
- 2 Fast Track clinics and 3 Extended Triage beds.

Hence, we don't see any issue in providing emergency care to any of the trial participants
if required.

*Shortcoming-V: Approval from Health Care Commission of Sindh need to be provided.*
**Response:**
SHCC was requested to visit Kharadar Hospital for Provisional License an application and Demand draft of Rs. 5000/- was submitted. SHCC has not been able to visit so far. However, they plan to visit Secondary Hospitals in due course of time. A Provisional License Application & DD for SHCC is attached for reference.

***Decision:***

*The CSC after detailed discussion and deliberation decided to defer the case for trial specific inspection & the Committee delegated the power to the Chairman CSC for constitution of the inspection panel to visit the site for verification/confirmation of required facilities & equipment required for Clinical Trial titled, "Can Esomeprazole Improve Outcomes in Women at High Risk of Pre-Eclampsia, a Phase-II, Placebo-Controlled, Randomized Multicenter Clinical Trial (The Espresso Study)". Nominated panel after inspection will generate a report which will be placed before the CSC for consideration.*

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**AGENDA ITEM XXVIII:**

**APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "CAN ESOMEPRAZOLE IMPROVE OUTCOMES IN WOMEN AT HIGH RISK OF PRE-ECLAMPSIA, A PHASE II, PLACEBO-CONTROLLED RANDOMIZED MULTICENTER CLINICAL TRIAL (THE ESPRESSO STUDY)", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F.No.03-13/2022 DD (PS)**

Application is from Dr. Sidrah Nausheen, Assistant Professor, Department of Obstetrics & Gynecology, The Aga Khan Hospital for Women & Children Kharadar, Atmaram Pritamdas Rd, near well come, Dharamsala Hamara Lyari, Karachi, Sindh dated 04th August, 2022, received on 19th August, 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. 7090456982, dated 03rd August, 2022. The trial is enlisted on U.S National Trial Registry with identification number ACTRN12618001755224 (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375343 )

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

i. **Sponsor:** The University of Sydney, Australia.

ii. **Funding Source**: National Health and Medical Research Council (NHMRC) Clinical Trials Centre, Australia

iii. **Contact information:** Prof Jon Hyett, +61295158777, jon.hyett@sydney.edu.au

**iv. Brief Summary/Purpose of trial:** The purpose of this study is to evaluate The risk of pre-eclampsia (elevated blood pressure in pregnancy) can be predicted through a screening test at 11-13+6 weeks' gestation. Previous work has shown that 'high risk' women benefit from taking aspirin through their pregnancy - resulting in a 62% reduction in pre-eclampsia prevalence before 37 weeks. Current treatment does not alter the prevalence of term pre-eclampsia (i.e. after 37 weeks). This study will test whether adding another treatment (esomeprazole) will cause a further reduction in blood pressure at the end of pregnancy. Pregnant women will take one esomeprazole or placebo tablet each day from before 16 weeks until delivery, in addition to aspirin, and will have their blood pressure measured throughout the study.

**v. Intervention/Exposure:**

| | |
|---|---|
| **Description of intervention(s) / exposure** | Esomeprazole 40mg oral tablet at night commencing prior to 16 weeks' gestation and continuing until delivery of pregnancy. Required background therapy is aspirin 150mg oral tablet at night commencing prior to 16 weeks' gestation and continuing until 36 weeks' gestation. Participants will be questioned on compliance at each visit, and a tablet count performed at 28 and 36 weeks |
| **Comparator / control treatment** | Placebo oral microcellulose tablet at night commencing prior to 16 weeks' gestation and continuing until delivery of pregnancy. Required background therapy is aspirin 150mg oral tablet at night commencing prior to 16 weeks gestation and continuing until 36 weeks gestation. |

**vi. Number of subjects to be recruited:** 200 Subjects will be enrolled on both sites of Pakistan.

**vii. Study design & details:**

| | |
|---|---|
| **Study Type :** | Interventional (Clinical Trial) |
| **Estimated Enrollment :** | 500 participants (Globally) |
| **Allocation:** | Randomized Controlled Trial |
| **Intervention Model:** | Parallel Assignment |
| **Masking:** | Quadruple Blinded (Participant, Care Provider, Investigator, Outcomes Assessor) |
| **Primary Purpose:** | Prevention |
| **Official Title:** | Can esomeprazole improve outcomes in women at high risk of pre-eclampsia? A phase II placebo-controlled randomised multi-centre clinical trial. The ESPRESSO Study |

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

Primary Outcome: Mean arterial pressure, measured by 24-hour ambulatory blood pressure (Time point: 36 weeks' gestation)

Secondary Outcome: MoM mean arterial pressure. The MoM (multiple of the median) of mean arterial pressure will be calculated by computing the ratio of observed mean arterial pressure to expected mean arterial pressure that would be anticipated for maternal characteristics at that specific gestational age. The measured mean arterial pressure will be calculated from a 24-hour ambulatory blood pressure record (see primary outcome measure). The expected mean arterial pressure will be derived from normative data reported in the literature (Time point: 36 weeks' gestation)

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

| S. No. | Document | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-II | Attached |
| 2 | Prescribed processing fee | Rs. 200,000/- deposited vide challan no. 7090456982, dated 03rd August, 2022. |
| 3 | Investigator Brochure (s) | Investigational Product Handling Manual is attached & informed that, in the ESPRESSO Study the approved product information for **esomeprazole** & **aspirin** will be utilised in place of Investigator's brochures. |
| 4 | Final protocol | Trial Protocol No. CTC 0179 ESPRESSO, Version 2.0, dated 06th June, 2018 is attached.<br>* Financing & insurance details are not provided |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached but following points need to be clarified<br>* Study is not insured & subjects need to file petition for compensation it need to be clarified & study should be insured. |
| 6 | List of participating countries | Australia & Pakistan.<br>* Details of Australia is not provided. |
| 7 | Phase of trial. | Phase – II |
| 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 approximate required quantity of following IMPs will be as follows:<br>i. Aspirin 300mg (Solprin®) Tablets (235 Packs 92s)<br>ii. Esomeprazole/Placebo 40mg Tablets (35 Tablets/bottle) (410 Bottles) |
| 9 | Site of the trial | i. Aga Khan University Hospital, Karachi.<br>ii. Aga Khan Hospital for Women & Children, Kharadar, Karachi.<br>* It is noted that, AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials |
| 10 | Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members. | AKUH IRB/ERC approval, dated 27th January, 2022, for a period of **one year** is attached.<br>**Note:** The composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval. |
| 11 | Approval of National Bio-ethics Committee (NBC) | Approval reference letter No.4-87/NBC-760/22/1688, dated 15th March, 2022 (for a period of **one** months).<br>**Note:** As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided. |
| 12 | CV's of the Investigators | CVs of following experts are attached. |

| | | |
|---|---|---|
| | | **xv.** Dr. Sidrah Nausheen (PI) (117-139/Corr.)<br>**xvi.** Dr. Sajid Sufi (Co-PI) (140-179/Corr.)<br>**xvii.** Dr. Shabina Ariff (Co-PI) (180-210/Corr.)<br>**xviii.** Dr. Lumaan Sheikh (Co-PI) (211-237/Corr.) |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | GMP Certificate(s) of following are need to be provided:<br>i. Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.<br>ii. Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India<br>iii. Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia<br><br>* GMP certificate of all manufacturer issued by respective country drugs regulatory body need to be provided.<br>** Further, connection & role of mentioned manufacturers need to be provided. |
| 14 | Pre-clinical/clinical safety studies | Attached. |
| 15 | Summary of Protocol | Attached. |
| 16 | Summary of Investigator Brochure | Summary of IB is attached only for esomeprazole manufactured by M/s Ranbaxy Australia |
| 17 | Adverse Event Reporting Form | Attached. |
| 18 | No of patients to be enrolled in each center. | 200 Subjects on both site in Pakistan.<br>Details regarding Subjects to be enrolled in Australia need to be provided. |
| 19 | Name of Monitors & Clinical Research Associate | Attached |
| 20 | Evidence of registration in country of origin. | TGA public summary is 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 | Approximately 03 Years. |
| 23 | Undertaking on Stamp paper | Attached. |

05. After initial scrutiny following shortcomings are recorded:

i. As per provided documents, composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval.

ii. As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.

iii. AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials.

iv. GMP certificate of following manufacturer issued by respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided.

a. Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.
b. Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India
c. Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia

v. Details regarding Subjects to be enrolled in Australia need to be provided.
vi. As per Informed Consent Form, the study is not insured & subjects need to file petition for compensation. It need to be clarified & study should be insured.
vii. Financing & insurance details is not incorporated in trial protocol.
viii. Anticipated cost of the [project need to be informed.

06. In the view of above, shortcoming letter was issued on 11th October, 2022, but still reply is awaited.

07. It is submitted that, the case was placed before CSC in its 35th meeting held on 13th October, 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 shortcomings as per Form-II of the Bio-Study Rules, 2017:*

*i. As per provided documents, composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval.*
*ii. As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.*
*iii. AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials.*
*iv. GMP certificate of following manufacturer issued by respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided.*

*a. Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.*
*b. Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India*
*c. Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia*

*v. Details regarding Subjects to be enrolled in Australia need to be provided.*
*vi. As per Informed Consent Form, the study is not insured & subjects need to file petition for compensation. It need to be clarified & study should be insured.*
*vii. Financing & insurance details is not incorporated in trial protocol.*
*viii. Anticipated cost of the project need to be informed.*

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

8. Accordingly, CSC decision communicated to applicant on 14th October, 2022, but yet response is awaited.

9. It is submitted that, the case was placed before CSC in its 36th 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 shortcomings as per Form-II of the Bio-Study Rules, 2017:*

*i. As per provided documents, composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval.*
*ii. As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.*

iii. *AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials.*

iv. *GMP certificate of following manufacturer issued by respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided.*

   a. *Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.*
   b. *Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India*
   c. *Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia*

v. *Details regarding Subjects to be enrolled in Australia need to be provided.*

vi. *As per Informed Consent Form, the study is not insured & subjects need to file petition for compensation. It need to be clarified & study should be insured.*

vii. *Financing & insurance details is not incorporated in trial protocol.*

viii. *Anticipated cost of the project need to be informed.*

*Further, applicant was given one last opportunity to provide requisite documents within 15 days positively, failing which the application will be liable to be rejected.*

10. CSC decision was communicated vide letter bearing number F.No.16-36/2022-CSC dated 25th November, 2022.

11. Reply from Dr. Sidrah Nausheen, Assistant Professor, Department of Obstetrics & Gynecology, The Aga Khan Hospital for Women & Children Kharadar, Atmaram Pritamdas Rd, near well come, Dharamsala Hamara Lyari, Karachi received on 09th December, 2022, in reference to this Division bearing even number dated 25th November, 2022.

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

| Sr. No. | Descriptions / Shortcomings | Reply | Remarks |
|---|---|---|---|
| 01 | As per provided documents, composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval. | We have received a fresh ERC approval dated 25th November 2022 the updated ERC committee follows the bio study rules 2017 NDCP guidelines the fresh ERC approval is attached for your review. | --- |
| 02 | As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided. | Fresh ERC and NBC approval dated 05th December, 2022 are attached for your review. | --- |
| 03 | AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials. | All the biological samples will be shipped to the sponsor which is the University of Sydney and there the analysis will take place and Material Transfer Agreement (MTA) for this purpose is in place and attached. | It is clarified that, blood samples of all 200 participants will be sent to designated laboratory for assay as |

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| | | | mentioned in MTA. |
| 04 | GMP certificate of following manufacturer issued by respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided.<br>a. Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.<br>b. Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India<br>c. Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia | ii. **Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC,3207, Australia.** Pharmaceutical Packaging Professionals PTY Ltd (PPP) is a supporter of the Australian and international pharmaceutical, biotechnology and medical research sectors. It provides GMP of investigational product manufacturing, logical services distribute clinical supplies to Australia, New Zealand, Asia, North America and Europe.<br>iii. **Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India** Esomeprazole RBX 40 mg is manufactured by Sun Pharma (manufacturer) - CoA is attached.<br>iv. **Akesa pty Ltd., 6114l Flinders Lane, Melbourne VIC 3000 Australia** Akesa Pharma is a supplier who provided Esomeprazole from the manufacturer (Sun Pharma) - Akesa is an approved supplier and I have attached Akesa's ISO 9001 certificate license to sell, or supply is attached. | Provided all GMP certificate are not issued by the respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided as per the bio Study Rules, 2017. |
| 05 | Details regarding Subjects to be enrolled in Australia need to be provided. | • ESPRESSO received ethics approval on 07th Dec 2017<br>• First patient was enrolled on 01st April2019<br>• The current enrolment is 190 patients<br>• The total sample size is 500 patients<br>• One of the most significant challenges was COVID-19 which has significantly | --- |

| | | | |
|---|---|---|---|
| | | delayed recruitment and site activations | |
| 06 | As per Informed Consent Form, the study is not insured & subjects need to file petition for compensation. It need to be clarified & study should be insured. | A revised consent form is attached the relevant section is highlighted for your review. | Attached consent form is not as per ICH-GCP guidelines & not safeguarding the rights of participants & there is nothing mentioned regarding Compensation/insurance for injuries or complications. Further, whenever ICF revised it should be provided in both English & local languages. |
| 07 | Financing & insurance details is not incorporated in trial protocol. | The relevant section of the protocol has been updated and attached for your review | Though relevant section in the trial protocol is revised but it is not informed in Pakistan what has been done for safety & insurance of participants. Further, it is informed that, previously Protocol No. CTC 0179 ESPRESSO, Version 2.0, dated 06th June, 2018 was attached & now revised protocol have Version 1.0 dated 18th October 2021. How it could be possible that, a [protocol is revised before it was directed to do so. Clarification in this regard needs to be provided. |
| 08 | Anticipated cost of the [project need to be informed. | A breakup of the cost is attached for your review. **(i.e.220,000 AUD)** | --- |

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

i. Provided all GMP certificate are not issued by the respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided as per the bio Study Rules, 2017.

ii. Attached consent form is not as per ICH-GCP guidelines & not safeguarding the rights of participants & there is nothing mentioned regarding Compensation/insurance for injuries or complications.
iii. Further, whenever ICF revised it should be provided in both English & local languages.

iv. Though relevant section in the trial protocol is revised but it is not informed in Pakistan what has been done for safety & insurance of participants. Further, it is informed that, previously Protocol No. CTC 0179 ESPRESSO, Version 2.0, dated 06th June, 2018 was attached & now revised protocol have Version 1.0 dated 18th October 2021. How it could be possible that, a protocol is revised before it was directed to do so. Clarification in this regard needs to be provided.

17. Accordingly, after approval shortcomings letter was issued on 2nd February, 2023, still response is awaited.

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

**Decision:**

*The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of following shortcoming:*

*i. Provided all GMP certificate are not issued by the respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided as per the bio Study Rules, 2017.*
*ii. Attached consent form is not as per ICH-GCP guidelines & not safeguarding the rights of participants & there is nothing mentioned regarding Compensation/insurance for injuries or complications.*
*iii. Further, whenever ICF revised it should be provided in both English & local languages.*
*iv. Though relevant section in the trial protocol is revised but it is not informed in Pakistan what has been done for safety & insurance of participants. Further, it is informed that, previously Protocol No. CTC 0179 ESPRESSO, Version 2.0, dated 06th June, 2018 was attached & now revised protocol have Version 1.0 dated 18th October 2021. How it could be possible that, a protocol is revised before it was directed to do so. Clarification in this regard needs to be provided.*

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**AGENDA ITEM XXIX:**

**APPROVAL AND REGISTRATION OF CLINICAL TRIAL TITLED, "A SINGLE CENTER, PLACEBO-CONTROLLED, ASCENDING SINGLE DOSE PHASE-I CLINICAL TRIAL TO EVALUATE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF RHN-001 IN HEALTHY ADULT VOLUNTEERS". F. No.03-03/2022-DD (PS)**

Application was submitted by Dr. Muhammad Raza Shah, (CNIC42201-4178970-1), General Manager, CBSCR, Dr. Panjwani Center for Molecular Medicine & Drug Research, International Center for Chemical & Biological Sciences, University of Karachi, dated 31st January 2022, wherein request has been made for registration & approval of subject Clinical Trial, which will be carried out at International Center for Chemical & Biological Sciences, University of Karachi, Karachi. Application is on prescribed Form-II, along with a fee of Rs.200000/- deposited vide challan no.2910530272.

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

**i. Name of Investigational product, including all available names; trade, generic or INN name etc.:**
   a. Generic Name: Salsalate (Micronized)

b. Trade Names: Anaflex, Salflex, Disalcid, Argesic-SA.

**ii. Sponsor:** WHO, Geneva Switzerland.

**iii. Purpose of trial defining the indication along with the anticipated cost of the project and sources of fund:**

Salsalate, is prescribed drug in the US since 1908 and the drug is tested and currently used by thousands of patients in many countries including US. RHN'001 Caplet contains Salsalate (Micronized) 750 mg which is a nonsteroidal anti-inflammatory (NSAID) agent for oral administration. Salsalate is the generic name of the prescription drug marketed under the brand names Disalcid, Salflex, Mono-Gesic, Salsitab, Anaflex etc. in various countries of the world.

The current study is designed to characterize the safety, tolerability and pharmacokinetics of a single dose of 750 mg RHN-001 compared to a single dose of 1500 mg RHN-001 in healthy adult volunteers.

COVID-I9 infected patients often develop a cough, fever, aches, and pain, as well as pneumonia. There is currently no U.S. Food and Drug Administration (FDA)-approved medication to treat COVID-l9 viral infections, or the common side effects associated with COVID-I9, including the fever, aches and pains. However, acetaminophen (for example, Tylenol) is commonly used to treat fever and aches associated with COVID-l9. RHN-001 is being developed for the treatment of mild to moderate COVID-I9 infection. Oral administration of RHN-001 is theorized to deliver a therapeutic dose of salsalate and its active medicine (salicylic acid) into the bloodstream and deliver its anti-inflammatory properties into the various parts of the body where inflammation has occurred due to the COVID-l9 virus.

This Trial is sponsored by RH Nanopharmaceuticals LLC, 140 Ocean Avenue, Monmouth Beach, NJ 07750, US7, which will bear the Cost (Estimated 300,000/= PKR) of this trial.

iv. **Investigating CRO:**

M/s International Center for Chemical & Biological Sciences, University of Karachi, Karachi.

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

| S. No. | Document | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-II | Attached. |
| 2 | Prescribed processing fee | Fee of Rs.200000/- paid vide challan number 9886981532, dated 07th December 2021 |
| 3 | Investigator Brochure (s) | Attached. |
| 4 | Final protocol | Protocol Version 1.0 attached.<br>*Details regarding financing & insurance as per ICH-GCP guidelines are not described / included in the protocol. |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached |
| 6 | List of participating countries | Pakistan only. |
| 7 | Phase of trial. | Phase-I |
| 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. | Salsalate Tablets (Micronized) 750 mg manufactured by M/s Pharms Ops, Inc., NJ, USA.<br>i. For trial use 100 Tablets<br>ii. Retention Samples 500 Tablets<br>iii. Total 600 Tablets.<br>* Justification required for quantity mentioned in reference to quantity to be utilized in trial. |
| 9 | Site of the trial | i. International Center for Chemical & Biological Sciences, University of Karachi, Karachi. (CTS-0046) |
| 10 | Institutional Review Board (IRB) approval of sites with complete | Attached. |

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| | composition of committee i.e. names and designation of members. | |
| 11 | Approval of National Bio-ethics Committee (NBC) | Attached.<br>Ref:No.4-87/NBC-729/22/1415, dated 27th January 2022. |
| 12 | CV's of the Investigators | CVs of following (P.I/Co-PI & others) are attached:<br>i. Principal investigator: Professor Dr. M. Raza Shah T.I. (Ph.D., Post Doc)<br>ii. Co-Principal investigator: Dr. Izhar Hasan (MD, Ph.D.)<br>iii. Clinical investigator: Dr. Syed Ali Talha Raza (MBBS)<br>iv. Technical Coordinator: Dr. Naghma Hashmi (Ph.D.)<br>v. Study Coordinator: Dr. Shafiullah (Ph.D., CCRP) |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | Not provided.<br>Attached certificate is from manufacturer itself, GMP Certificate for M/s Pharms Ops, Inc., NJ, USA issued by the Drugs Regulatory Authority of the country of origin (US FDA) need to be provided. |
| 14 | Pre-clinical/clinical safety studies | Attached. |
| 15 | Summary of Protocol | Attached. |
| 16 | Summary of Investigator Brochure | Not provided. |
| 17 | Adverse Event Reporting Form | Attached. |
| 18 | No of patients to be enrolled in each center. | 32 Subjects in each period.<br>Total subjects 64 |
| 19 | Name of Monitors & Clinical Research Associate | i. Dr. Muhammad Imran (Ph.D. in Pharmacy), M/s Global Scientific R&D Pvt Ltd., Karachi. |
| 20 | Evidence of registration in country of origin. | Not provided.<br>PI need to provide details regarding brand of IMP utilized in the trial which is manufactured by M/s Pharms Ops, Inc., NJ, USA |
| 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 | Approximately 01 Month |
| 23 | Undertaking on Stamp paper | Attached. |

04. After initial scrutiny following shortcomings observed:

v. Details regarding financing/source of funding of the trial & insurance of trial participants as required by ICH-GCP guidelines are not described/included in the protocol. Applicant need to revise/amend study protocol & incorporate required details & submit revised protocol along with IRB & NBC approvals.

vi. Justification required for quantity mentioned in reference to quantity to be utilized in trial.

vii. Attached certificate as a GMP certificate, is from manufacturer itself, GMP Certificate for M/s Pharms Ops, Inc., NJ, USA issued by the Drugs Regulatory Authority of the country of origin (US FDA) need to be provided.

viii. PI need to provide details regarding brand of IMP utilized in the trial which is manufactured by M/s Pharms Ops, Inc., NJ, USA.

ix. As informed by the applicant that, there are different brands are available in the market. So CoPP or Free sale certificate need to be provided.

x. Estimated cost of the project is not factual/justifiable.

05. Accordingly, shortcomings were communicated to applicant on 28th January, 2022.

06. Applicant submitted reply in reference to this Division letter bearing even number dated 28th January, 2022 & summary of submitted reply along with attachments is as follows:

<table>
<tr><th>Sr.</th><th>Descriptions / Shortcomings</th><th>Reply</th><th>Remarks</th></tr>
<tr><td>01</td><td>Details regarding financing/source of funding of the trial & insurance of trial participants as required by ICH-GCP guidelines are not described/included in the protocol. Applicant need to revise/amend study protocol & incorporate required details & submit revised protocol along with IRB & NBC approvals.</td><td>The protocol has mentioned "RH Nanopharmaceuticals LLC, 140 Ocean Avenue, Monmouth Beach, NJ 07750, USA" as the sponsor of the Trial which will bear the expenses of the trial. Corrected page (Appendix-2) of Form-II of the Bio-study Rule 2017 is attached herein as appendix-1 with approximate cost of the study as 30,00,000/= PKR. The Informed Consent Form which is an integral part of the study mention the insurance of Trial Participants in clause <u>3. In Case of Research Related injuries.</u><br><br>The section of the ICH-GCP guideline states to mention Financing and insurance if not addressed in a separate agreement. We have draft insurance (Attached) and separate study agreement with sponsor which describe full financial details.</td><td>It was informed & advised to revise/amend study protocol & incorporate required details & submit revised protocol along with IRB & NBC approvals. But applicant submitted explanation only but not submitted revised protocol.</td></tr>
<tr><td>02</td><td>Justification required for quantity mentioned in reference to quantity to be utilized in trial.</td><td>The Actual Drug/ Placebo quantity used in the trial is 96 Tablets with following distribution:<br><table><tr><td rowspan="2">Cohort</td><td>A1=16 Tablets</td><td rowspan="4">Total=96 Tablets</td></tr><tr><td>A2=16 Tablets</td></tr><tr><td rowspan="2">Cohort</td><td>B1=32 Tablets</td></tr><tr><td>B2=32 Tablets</td></tr></table>As per the FDA Guideline (Retention of Bioavailability and Bioequivalence Testing Samples; available online), The study sponsor or contract research organization will retain a sufficient quantity of each reserve sample of the test article and of the reference standard to permit FDA to perform five times all of the release tests required in the NDA, ANDA, or supplemental application. In addition, each reserve sample is required to be: (1) Adequately identified so that it can be positively identified as having come from the same sample as used in the specific bioavailability or bioequivalence study, (2) stored under specified</td><td>---</td></tr>
</table>

| | | | |
|---|---|---|---|
| | | conditions, and (3) retained for a specified period.<br>Thus, approximately 500 Tablets will be archived in the trial center for a period of 5 years. | |
| 03 | Attached certificate as a GMP certificate, is from manufacturer itself, GMP Certificate for M/s Pharms Ops, Inc., NJ, USA issued by the Drugs Regulatory Authority of the country of origin (US FDA) need to be provided. | The sponsor has submitted an IND application to FDA and US-FDA does not provide any GMP certification for the product in development. Based on the IND application and data of final drug manufacturing documents, including this GMP certificate from the manufacturing organization i.e. pharm ops, they have been given permission to conduct the study (Attached appendix- 2). pharm ops is registered with FDA as a GMP abiding Establishment and FDA maintain these registrations on line. I have attached here a history of Pharm Ops Registration with FDA, the facility has an FEI # 3002626861 and a DUNS # 079851746. Appendix 3 | It is informed again that, GMP Certificate for M/s Pharms Ops, Inc., NJ, USA issued by the Drugs Regulatory Authority of the country of origin (US FDA) need to be provided, which is a regulatory requirement under the Bio-Study Rules, 2017. Further, it is clarified that, GMP certificate is issued for manufacturing facility not for a product. |
| | Attached GMP certificate is from the manufacturer itself GMP from Regulatory Authority of the Country of Origin (i.e. US-FDA) is required. | The sponsor has submitted IND application to FDA and FDA allowed them to conduct the clinical trial (Appendix 1). FDA reviews the submitted IND to determine whether the phase I investigational drug to be used in the clinical trial is sufficiently safe to permit the trial to proceed. This determination is based, in part on whether the investigational product has the identity, strength, quality, and purity, and purported effect described in the IND application (Please refer to Guidance for Industry cGMP for Phase I Investigational Drugs. Page 3).<br>In addition, as per the FDA guidance document on Providing Regulatory Submissions in Electronic Format - Drug Establishment Registration and Drug Listing. the owner or operator of an establishment entering into the manufacture, preparation, propagation, compounding, or processing (which includes, among other things, repackaging and relabeling) of a drug or drugs must register the establishment with FDA within 5 days after beginning the operation. Pharm Ops (Manufacturer of the drug to be used in the trial) is registered with FDA as a GMP abiding Establishment and FDA maintain these registrations on line. I have attached here the screenshot of Pharm Ops Establishment Registration with FDA, the facility has an FEI # 3002626861and a DUNS # 079851746 (Appendix 2). | It is informed again that, GMP Certificate for M/s Pharms Ops, Inc., NJ, USA issued by the Drugs Regulatory Authority of the country of origin (US FDA) need to be provided, which is a regulatory requirement under the Bio-Study Rules, 2017. Further, it is clarified that, GMP certificate is issued for manufacturing facility not for a product. |

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|---|---|---|---|
| 04 | PI need to provide details regarding brand of IMP utilized in the trial which is manufactured by M/s Pharms Ops, Inc., NJ, USA. | The brand used in this trial is RHN-001 (Micronized Salsalate, 750mg). The details of the ingredients used in the Trial batch (No. 78631221) is given in appendix 4. All excipients used in the formulation are commonly used excipients for tablets and have been used in several commercially available products approved by FDA. | It is again informed that, applicant mentioned following brand names in the application as trade names of the IMP:<br>i. Anaflex<br>ii. Salflex<br>iii. Disalcid<br>iv. Argesic-SA<br>So, applicant again advised to clarify which of the Brand they want to use un the trial with ode name of RHN-001 |
| 05 | As informed by the applicant that, there are different brands are available in the market. So CoPP or Free sale certificate need to be provided. | Yes, there are different brands of Salsalate available in U.S., However, we are not using those brands in this trials. Therefore, we request for exemption of CoPP or Free Sale Certificate for those brands. | As the product brands available in market so CoPP for IMP may not be exempted, as it's a regulatory requirement under the Bio-Study Rules, 2017. |

07. After evaluation of reply following shortcomings still need to be clarified:

i. It was informed & advised to revise/amend study protocol & incorporate required details & submit revised protocol along with IRB & NBC approvals. But applicant submitted explanation only but not submitted revised protocol.

ii. It is informed again that, GMP Certificate for M/s Pharms Ops, Inc., NJ, USA issued by the Drugs Regulatory Authority of the country of origin (US FDA) need to be provided, which is a regulatory requirement under the Bio-Study Rules, 2017. Further, it is clarified that, GMP certificate is issued for manufacturing facility not for a product.

iii. It is again informed that, applicant mentioned following brand names in the application as trade names of the IMP:
   a. Anaflex
   b. Salflex
   c. Disalcid
   d. Argesic-SA

   So, applicant again advised to clarify which of the Brand they want to use un the trial with ode name of RHN-001

iv. As the product brands available in market so CoPP for IMP may not be exempted, as it's a regulatory requirement under the Bio-Study Rules, 2017.

08. The application was placed before CSC in its 36th 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. It was informed & advised to revise/amend study protocol, incorporate required details & submit revised protocol along with IRB & NBC approvals. The applicant submitted explanation only but not submitted revised protocol.*

ii. *It is informed again that, GMP Certificate for M/s Pharms Ops, Inc., NJ, USA issued by the Drugs Regulatory Authority of the country of origin (US FDA) need to be provided, which is a regulatory requirement under the Bio-Study Rules, 2017. Further, it is clarified that, GMP certificate is issued for manufacturing facility not for a product.*

iii. *It is again informed that, applicant mentioned following brand names in the application as trade names of the IMP:*
   a. *Anaflex*
   b. *Salflex*
   c. *Disalcid*
   d. *Argesic-SA*

   *So, applicant is again advised to clarify which of the brand they want to use in the trials with code name of RHN-001*

iv. *As the product brands are available in market so CoPP for IMP may not be exempted, as it's a regulatory requirement under the Bio-Study Rules, 2017.*

v. *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.*

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

*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. 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.*

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

10. Reply 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. Wherein reply is in reference to this Division letter bearing even number dated 25th November, 2022.

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

| Sr. | Descriptions / Shortcomings | Reply | Remarks |
|---|---|---|---|
| i. | It was informed & advised to revise/amend study protocol, incorporate required details & submit revised protocol along with IRB & NBC approvals. The applicant submitted explanation only but not submitted revised protocol. | Please find the revised study protocol with required changes, IRB and NBC approvals for the revised version of protocol attached in **(Annexure-I) (Page 288-375/Corr.)** | Revised Protocol Version 2.0 attached along with IRB & NBC approvals |
| ii. | It is informed again that, GMP Certificate for M/s Pharms Ops, Inc., NJ, USA issued by the Drugs Regulatory Authority of the country of origin (US FDA) need to be provided, which is a regulatory requirement under the Bio-Study Rules, 2017. Further, it is clarified | In USA the owner or operator of an establishment entering in to the manufacture, preparation, propagation, compounding or processing (which includes, among other things, repackaging & relabeling) of a drug or drugs must register the establishment with FDA within 5 days after beginning the operation. Pharm Ops (Manufacturer of drugs to be used in the trial) is registered with FDA as a GMP abiding Establishment and FDA maintain these | GMP Certificate is not provided. |

| | | | |
|---|---|---|---|
| | that, GMP certificate is issued for manufacturing facility not for a product. | registrations online. I have attached here the screen shot of Pharm Ops Establishment Registration with FDA, the facility has an FEI # 3002626861 and a DUNS # 079851746 **(Annexure-II) (Page 377/Corr.)** | |
| iii. | It is again informed that, applicant mentioned following brand names in the application as trade names of the IMP:<br>a. Anaflex<br>b. Salflex<br>c. Disalcid<br>d. Argesic-SA<br>So, applicant is again advised to clarify which of the brand they want to use in the trials with code name of RHN-001 | Salsalate is available with the names Anaflex, Salflex, Disalcid, Argesic-SA (internet sources) and around 38 different companies are manufacturing this drug in USA having 500mg and 750mg strengths as generics(https://www.accessdata.fda.gov/scripts /cder/ndc/dsp_searchresult.cfm). The API used in this trial is also Salsalate, however it is in micronized form. The commercial formulation of micronized salsalate is not available. This clinical trial is planned to evaluate the effect of micronization on absorption, pharmacokinetic and tolerability in healthy human subjects. The sponsor Call it RHN-001 for now and its trade name will be decided after approval.<br>The above names were mentioned in the protocol to describe uses of salsalate in literature and establish a ground for the introduction. The PI do not have any intention to use the above mentioned brands in this trial. The aforementioned brands of salsalate are available in literature and these were mentioned in the application for introduction purposes. Please find the corrected **Appendix-I** page for application attached as **Annexure-III** with this letter. | From submitted reply it can't be clarified that, who & where micronized Salsalate produced for the trial. |
| iv. | As the product brands are available in market so CoPP for IMP may not be exempted, as it's a regulatory requirement under the Bio-Study Rules, 2017. | We are not using any of the mentioned brands in this trial. The Drug used in this Trial is RHN-001 (Micronized Salsalate). The trial is designed to evaluate, safety, tolerability and pharmacokinetics of the RHN-001 (micronized Salsalate) administered as 750mg (one Tablet) and 1500 mg (two×750mg Tablets) in healthy adults under fed and fasted states. | --- |
| v. | 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. | We appreciate the respected CSC members' comments and justification about the PI background. As per the FDA, 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"<br><br>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 | --- |

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| | | (or dental) decisions are always the responsibilities of physician in our set-up.<br>According to FDA's Information Sheet Guidance for Sponsors (Annexure-4), Clinical Investigators, and IRBs Frequently Asked Questions, the FDA response to "Must the investigator be a physician?" is given below:<br><br>The regulations do not require that the investigator be a physician. Sponsors are required to select only investigators qualified by training and experience as appropriate experts to investigate the drug (21 CFR 312.53(a)). In the event the clinical investigator is a non-physician, a qualified physician (or dentist, when appropriate) should be listed as a sub-investigator for the trial and should be responsible for all trial-related medical (or dental) decisions. (ICH E6 section 4.3.1;<br><br>http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/uc m073122.pdf).<br>FDA further states in response to another question "What are the minimum qualifications of an investigator?" as below:<br><br>As stated in #4, the regulations require that sponsors select investigators who are qualified by training and experience as appropriate experts to investigate the drug. The regulations do not specify the minimum requirements nor do the regulations specify what qualifications an investigator must have in order to be considered qualified by training and experience to conduct a clinical investigation. Sponsors have discretion in determining what qualifications, training, and experience will be needed, based on the general recognition that this would include familiarity with human subject protection (HSP) regulations (i.e., 21 CFR Parts 50 and 56) and practices as well as good clinical practice (GCP) regulations (see 21 CFR Part 312) and standards (e.g., ICH E6) for the conduct of clinical studies.<br><br>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 PI of this study led the DRAP and NBC-approved Phase 1 clinical trial of the Sinopharm Vaccine in Pakistan and successfully completed.<br><br>In addition, the followings are the credentials of PI related to Clinical Research that reflects the clinical background of PI: | |

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|---|---|---|---|
| | | The Pl 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 (Annexure-5. NBC letter, DRAP letter, Publication)<br><br>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" (Annexure-6: NBC approval, DRAP approval)<br><br>The PI of this study also remained PI 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." (Annexure-7. NBC approval, DRAP approval)<br><br>The PI 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. (Annexure-8. List of BE/BE, PK studies and approvals conducted by PI)<br><br>The PI of this study has participated in several GCP and GLP training courses needed to act as Pl.<br><br>(Annexure-9. Training certificates of PI).<br>The PI of this study has published more than 200 research articles in the area of Drug Delivery and Nano-medicine through which the PI 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 | |

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|---|---|---|---|
| | | (Annexure-10.)<br><br>The PI 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 (Annexure-11) is given below i.e.<br><br>i. Lipid-Based Nano carriers for Drug Delivery and Diagnosis, Paperback ISBN: 9780323527293<br>ii. Nano carriers for Cancer Diagnosis and Targeted Chemotherapy Paperback ISBN: 9780128167731<br>iii. Metal Nanoparticles for Drug Delivery and Diagnostic Applications Paperback ISBN: 9780128169605<br>iv. Nano carriers for Organ-Specific and Localized Drug Delivery Paperback ISBN: 9780128210932 | |

12. After evaluation of reply following shortcomings still need to be clarified:

i. It is informed again that, GMP Certificate for M/s Pharms Ops, Inc., NJ, USA issued by the Drugs Regulatory Authority of the country of origin (US FDA) need to be provided, which is a regulatory requirement under the Bio-Study Rules, 2017. Further, it is clarified that, GMP certificate is issued for manufacturing facility not for a product.
ii. Further, authorization or other evident document required which empower M/s Pharm Ops for manufacture of IMP (RHN-001) Salsalate Micronized Tablets.

13. Accordingly, shortcomings were communicated vide letter bearing even number dated 31st January, 2023, still response is awaited.

14. Further, in reference to 36th CSC Meeting decision for the subject application, the Chairman CSC nominated following panel for inspection & letter was communicated on dated 08th December, 2022:

i. Dr. Fazal Subhan, CSC Member/ Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar.
ii. Dr. Saif Ur Rehman Khattak, In-Charge CDL, Karachi.
iii. Dr. Mirza Tasawer Baig, CSC Member/ Associate Professor & Clinical Pharmacist, Dr. Ziauddin Hospital, Karachi.
iv. Dr. Ahson Siddiqui, CEO-Sindh Health Care Commission, Karachi.
v. Shafqat Hussain Danish, Assistant Director (Clinical Research), Pharmacy Services Division, DRAP.

15. Accordingly, experts panel inspected the subject site on 26th December, 2022 & submitted inspection report with following remarks:

*Concluding status of inspection / application*

- **Recommended for approval**

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

17. 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 as follows:

a. to approve the Phase-I Clinical Trial titled, "A Single Center, Placebo-Controlled, Ascending Single Dose Phase-I Clinical Trial to Evaluate Safety, Tolerability and Pharmacokinetics of RHN-001, in Healthy Adult Volunteers" under the Bio-Study Rules, 2017, to be conducted at International Center for Chemical & Biological Sciences, University of Karachi, Karachi. (CTS-0046).
b. Approval letter will be issued after compliance of following points:
    i. provision/clarification regarding GMP Certificate of IMP manufacturer (whether available on line or provided by PI).
    ii. Inclusion of a clinician in the trial as Co-Principal Investigator.
c. 600 tablets (100 for trial and 500 for retention sample) of IMP i.e. Salsalate Tablets (Micronized) 750 mg manufactured by M/s Pharms Ops, Inc., NJ, USA, will imported after getting necessary approval/NOC from concerned DRAP field office.

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**AGENDA ITEM XXX:**

**APPLICATION FOR APPROVAL OF A PHASE-I CLINICAL TRIAL TITLED, "OPEN-LABEL, PHASE I CLINICAL STUDY TO DETERMINE THE SAFETY AND PRELIMINARY IMMUNOGENICITY OF SARS-COV-2 VARIANT MRNA VACCINE (LVRNA010) IN HEALTHY PARTICIPANTS AGED 18 YEARS AND OLDER", FROM CBSCR-ICCBS, KARACHI. F. No.03-16/2022-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 21st 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. 25374011894, dated 18th November, 2022. The trial is also enlisted on U.S National Trial Registry with identification number ***NCT05599802*** *(https://www.clinicaltrials.gov/ct2/show/NCT05599802 )*

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

i. **Sponsor:** M/s AIM Vaccine Co., Ltd. China.
ii. **Collaborators:**
    a. Ningbo Rongan Biological Pharmaceutical Co., Ltd.
    b. Live RNA Therapeutics Inc.
iii. **Purpose of trial:** This is an open-label, randomized study to determine the safety and preliminary immunogenicity of mRNA SARS-CoV-2 Vaccine (LVRNA010) in people aged 18 years and older.

**iv. Arms & Interventions:**

| S.No. | Investigational Product | Control Product |
|---|---|---|

| | | |
|---|---|---|
| 01 | Experimental: 1A: 50µg SARS-CoV-2 variant mRNA vaccine Participants who have not received any COVID-19 vaccines will vaccinate two doses of study vaccine with 28 days apart. | Biological: SARS-CoV-2 variant mRNA vaccine low dose 50µg/dose |
| 02 | Experimental: 1B: 100µg SARS-CoV-2 variant mRNA vaccine Participants who have not received any COVID-19 vaccines will vaccinate two doses of study vaccine with 28 days apart. | Biological: SARS-CoV-2 variant mRNA vaccine high dose 100µg/dose |
| 03 | Experimental: 2A: 50µg SARS-CoV-2 variant mRNA vaccine Participants who have received 2 dose of COVID-19 inactivated vaccines will vaccinate 1 doses of study vaccine. | Biological: SARS-CoV-2 variant mRNA vaccine low dose 50µg/dose |
| 04 | Experimental: 2B: 100µg SARS-CoV-2 variant mRNA vaccine Participants who have received 2 dose of COVID-19 inactivated vaccines will vaccinate 1 doses of study vaccine. | Biological: SARS-CoV-2 variant mRNA vaccine high dose 100µg/dose |
| 05 | Experimental: 3A: 50µg SARS-CoV-2 variant mRNA vaccine Participants who have received 2 dose of COVID-19 mRNA vaccines will vaccinate 1 doses of study vaccine. | Biological: SARS-CoV-2 variant mRNA vaccine low dose 50µg/dose |
| 06 | Experimental: 3B: 100µg SARS-CoV-2 variant mRNA vaccine Participants who have received 2 dose of COVID-19 mRNA vaccines will vaccinate 1 doses of study vaccine. | Biological: SARS-CoV-2 variant mRNA vaccine high dose 100µg/dose |

**v. Details regarding IMPs & required quantity along with justification:**

**A. Active:** SARS-CoV-2 variant mRNA vaccine (LVRNA010)

**Dosage Form:** Injection.

**B. Quantity required:**

| **Dosage** | **Group** | **Arm** | **Dose(s) of IMP in each arm** | **No. of Subjects in each arm** | **Total IMP in each arm** | **Total** |
|---|---|---|---|---|---|---|
| 50µg | 1 | Arm-1 | 2 doses | 24 | 48 | 111 |
| | 2 | Arm-1 | 1 dose | 24 | 24 | |
| | 3 | Arm-1 | 1 dose | 24 | 24 | |
| | Quantity of retention Samples/doses | | | | 15 | |
| **Dosage** | **Group** | **Arm** | **Dose(s) of IMP in each arm** | **No. of Subjects in each arm** | **Total IMP in each arm** | **Total** |
| 100µg | 1 | Arm-2 | 2 doses | 24 | 48 | 111 |
| | 2 | Arm-2 | 1 dose | 24 | 24 | |
| | 3 | Arm-2 | 1 dose | 24 | 24 | |
| | Quantity of retention Samples/doses | | | | 15 | |

**vi. Number of subjects to be recruited:** **144** Subjects (Phase-I only in Pakistan)

**vii. Anticipated cost of the project:** USD 72,000/-

**viii. Study design & details:**

| | |
|---|---|
| **Study Type :** | Interventional (Clinical Trial) |
| **Estimated Enrollment :** | 144 participants |
| **Allocation:** | Randomized |
| **Intervention Model:** | Parallel Assignment |
| **Masking:** | None (Open Label) |
| **Primary Purpose:** | Prevention |
| **Official Title:** | An Open-Label, Phase 1 Clinical Study to Determine the Safety and Preliminary Immunogenicity of SARS-CoV-2 Variant mRNA Vaccine (LVRNA010) in Healthy Participants Aged 18 Years and Older |

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

**Primary Outcome Measures:**

i. Incidence, severity, and duration of each solicited (local and systemic) AE. [ Time Frame: Within 30 minutes and 7 days after (each dose of) vaccination]
ii. Incidence, severity, and duration of each unsolicited AE. [ Time Frame: Within 28 days after (each dose of) vaccination]
iii. The percentage of participants with abnormal hematology and chemistry laboratory values. [ Time Frame: 4 days after (each dose of) vaccination]

**Secondary Outcome Measures:**

i. Geometric Mean Titer (GMT) of SARS-CoV-2 Virus Neutralizing Antibody (VNA) (live virus assay). [ Time Frame: Before (each dose of) vaccination, 14 days and 28 days after (each dose of) vaccination]
ii. Seroconversion Rate (SCR) of SARS-CoV-2 Virus Neutralizing Antibody (VNA) (live virus assay). [ Time Frame: Before (each dose of) vaccination, 14 days and 28 days after (each dose of) vaccination]
iii. Geometric Mean Increase (GMI) of SARS-CoV-2 Virus Neutralizing Antibody (VNA) (live virus assay). [ Time Frame: Before (each dose of) vaccination, 14 days and 28 days after (each dose of) vaccination]
iv. GMT of S-protein specific IgG antibodies (ELISA) [ Time Frame: Before (each dose of) vaccination, 14 days and 28 days after (each dose of) vaccination]
v. SCR of S-protein specific IgG antibodies (ELISA) [ Time Frame: Before (each dose of) vaccination, 14 days and 28 days after (each dose of) vaccination]
vi. GMI of S-protein specific IgG antibodies (ELISA) [ Time Frame: Before (each dose of) vaccination, 14 days and 28 days after (each dose of) vaccination]
vii. The incidence, severity, and causality of Serious Adverse Events (SAEs) [ Time Frame: Within 12 months after (full) vaccination]
viii. The incidence, severity, and causality of Adverse Events of Special Interest (AESI) [ Time Frame: Within 12 months after (full) vaccination]
ix. The incidence, severity, and causality of the occurrence of pregnancy events [ Time Frame: Within 12 months after (full) vaccination]

**Other Outcome Measures:**

i. GMT of SARS-CoV-2 VNA (live virus assay). [ Time Frame: 3 months and 6 months after (full) vaccination]
ii. SCR of SARS-CoV-2 VNA (live virus assay). [ Time Frame: 3 months and 6 months after (full) vaccination]
iii. GMI of SARS-CoV-2 VNA (live virus assay). [ Time Frame: 3 months and 6 months after (full) vaccination]
iv. GMT of S-protein specific IgG antibodies (ELISA) [ Time Frame: 3 months and 6 months after (full) vaccination]
v. SCR of S-protein specific IgG antibodies (ELISA) [ Time Frame: 3 months and 6 months after (full) vaccination]
vi. GMI of S-protein specific IgG antibodies (ELISA) [ Time Frame: 3 months and 6 months after (full) 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. 25374011894, dated 18th November, 2022. |
| 3 | Investigator Brochure (s) | IB Version 1.0 dated 17th August, 2022 is attached. |
| 4 | Final protocol | Three protocols are attached<br>Protocol No. LVRNA009-I-01<br>Version 1.0, dated 25th January, 2022 (Titled-A Phase I clinical trial to evaluate the safety, tolerability and preliminary immunogenicity of the SARS-CoV-2 mRNA vaccine (LVRNA009) in Chinese people aged 18 years and older) for study purpose- To evaluate the safety and tolerability ofLVRNA0O9 in healthy Chinese population aged 18<br>years and older; on 72 Subjects<br>Protocol No. LVRNA009-II-01<br>(Titled-A Phase II clinical trial to evaluate the immunogenicity and safety of the SARS-CoV-2 mRNA vaccine (LVRNA009) in Chinese population aged 18-59 years)<br>Protocol No. CRO-012 -VAC -( SARS- CoV-2 mRNA Phase-I)-2022/Protocol/1.0<br>Version 1.0, dated 20th September, 2022 (Prepared by PI & not signed by the Sponsor)<br>* Reimbursement & Insurance policy not covering for their time, lost wages, or any inconvenience experienced during scheduled study visits. It is also mentioned that, the study team will not pay for long-term treatment of unrelated conditions diagnosed during the trial & it is not ethical for Phase-I Clinical trial. Furthermore, details / procedure for trial related health injury compensation is need to be clarified & should be incorporated in trial protocol.<br>** Attached protocol is not as per ICH-GCP Guidelines.<br><br>*** IMP code is different in attached protocol.<br>**** Details regarding Samples shipment (designated courier services), to designated Bio-Analytical Laboratory (not mentioned) further MTA is also not provided. |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached.<br>It is mentioned in ICF that, Sponsor is not responsible for the negligence or willful misconduct of study doctor or the study site, clarification in this regard is required that, who will be responsible then & there is no details regarding insurance is shared with application.<br>In the ICF form contact details of PI are mentioned but study doctor/clinician contact details should also be included as PI is not a Clinician. |
| 6 | List of participating countries | China & Pakistan. |

| | | |
|---|---|---|
| | | * Clarification required why Phase-I trial being conducted only in Pakistan & not in the Country of origin. |
| 7 | Phase of trial. | Phase – I |
| 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:<br>• 50µg =111 Doses<br>• 100µg=111 Doses |
| 9 | Site of the trial | i. Center for Bioequivalence Studies and Clinical Research (CBSCR) ICCBS, University of Karachi, Pakistan. (CTS-0046) |
| 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-052//2022, dated 11th October, 2022. (CBSCR-ICCBS) |
| 11 | Approval of National Bio-ethics Committee (NBC) | Reference No.4-87/COVID-121/22/609, dated 15th November, 2022 (for a period of **Six** months). |
| 12 | CV's of the Investigators | CVs of following experts are attached.<br>**xix.** Prof. Dr. Muhammad Raza Shah (PI)<br>Details regarding any clinician (who will be responsible of Clinical part of the trial) is not provided |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | Following documents are attached:<br>i. COA of IMP attached but the batch mentioned in COA will expired on 4th July, 2023<br>ii. GMP Certificate of Ningbo Rongan Biological Pharmaceutical Co. Ltd., China is attached<br>iii. As mentioned in application that, the product is on IND stage in China & CoPP can't be provided. So, it is requested to provide IND issued in China. |
| 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. | 144 Subjects<br>Clarification required why Phase-I trial being conducted only in Pakistan & not in the Country of origin. |
| 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<br>Batch Certificate for Investigational Product issued by manufacturer is attached.<br>* GMP Certificate of IMP manufacturer is not provided. |

| | | |
|---|---|---|
| | | ** CoPP for control product COMIRNATY ® (BNT162b2) & GMP Certificate of its manufacturer: Pfizer is not provided.<br><br>**Public notice issued by China State Drug Administration body is attached with clarification regarding non-issuance of GMP Certificate (Page 281-285/Corr.)** |
| 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 | **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, still response is awaited.

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

08. 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 as follows:

a. to approve the Phase-I Clinical Trial titled, "Open-Label, Phase I Clinical Study to Determine the Safety and Preliminary Immunogenicity of SARS-CoV-2 Variant MRNA Vaccine (LVRNA010) in Healthy Participants aged 18 Years and Older", under the Bio-Study Rules, 2017, to be conducted at International Center for Chemical & Biological Sciences, University of Karachi, Karachi. (CTS-0046).

b. Approval letter will be issued after inclusion of a clinician in the trial as Co-Principal Investigator

d. A total of 144 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.:

**Active:** SARS-CoV-2 variant mRNA vaccine (LVRNA010)
**Dosage Form:** Injection.

| Dosage | Group | Arm | Dose(s) of IMP in each arm | No. of Subjects in each arm | Total IMP in each arm | Total |
|---|---|---|---|---|---|---|

| | | | | | | |
|---|---|---|---|---|---|---|
| 50µg | 1 | Arm-1 | 2 doses | 24 | 48 | 111 |
| | 2 | Arm-1 | 1 dose | 24 | 24 | |
| | 3 | Arm-1 | 1 dose | 24 | 24 | |
| | Quantity of retention Samples/doses | | | | 15 | |
| **Dosage** | **Group** | **Arm** | **Dose(s) of IMP in each arm** | **No. of Subjects in each arm** | **Total IMP in each arm** | **Total** |
| 100µg | 1 | Arm-2 | 2 doses | 24 | 48 | 111 |
| | 2 | Arm-2 | 1 dose | 24 | 24 | |
| | 3 | Arm-2 | 1 dose | 24 | 24 | |
| | Quantity of retention Samples/doses | | | | 15 | |

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**AGENDA ITEM XXXI:**

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

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

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

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

### E. 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<br>IB of control product Comirnaty manufactured by Pfizer is not provided. |
| 4 | Final protocol | Attached<br>Protocol No. CRO-011-VAC-(SARS-CoV-2 mRNA Phase III)-2022/Protocol/1.0<br>Version 1.0, dated 13th September, 2022<br><br>* 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:<br><br><u>Study Vaccine COVID-19 mRNA Vaccine (RBMRNA-405)</u><br>• Sponsor: Argorna Pharmaceuticals Co., Ltd<br>• Manufacturing: Guangzhou RiboBio Co., Ltd<br>• Specification: 1.0ml/vial; 0'2mg/ml (0'3ml each dose; one vial for three)<br>• Total no. of vaccine doses:750<br>• Total no. of vials for volunteers: 750/3: **250** vials<br>• Retention doses for archiving: 30<br>• Total no. of vials for retention: 30/3= 10 vials<br>• Total no. of vials for volunteers + Total no. of vials for retention=250+10=**<u>260 vials</u>**<br><br><u>Control Vaccine Comirnaty ® (BNT162b2)</u><br>• 0.3m1 each dose - 1 vial for five<br>• Total no. of vaccine doses: 750<br>• Total no. of vials for volunteers: 750/5: **150** vials<br>• Retention doses for archiving: 30<br>• Total no. of vials for retention: 30/5: 6 vials<br>• Total no. of vials for volunteers + Total no. of vials for retention = 150 + 6 = **<u>156 vials</u>** |
| 9 | Site of the trial | ii. Center for Bioequivalence Studies and Clinical Research (CBSCR) ICCBS, University of Karachi, Pakistan. (CTS-0046)<br>iii. Creek General Hospital Ibrahim Haidery, Korangi Creek, Karachi. (CTS-0077) |

| | | |
|---|---|---|
| | | iv. 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. | ii. Ref: # ICCBS/CBSCR/IEC/LET-051/2022, dated 11th October, 2022. (CBSCR-ICCBS)<br>iii. Ref: # PIH/IRB LET-001/2022, dated 24th October, 2022. (Pak International Hospital, Karachi)<br>iv. 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.<br>**xx.** Prof. Dr. Muhammad Raza Shah (PI) (162-166/Corr.)<br>**xxi.** Dr. Naveed Yunus (Site-PI-CBSCR) (167-170/Corr.)<br>**xxii.** Dr. Muhammad Iqbal Afridi (Site-PI-Pak International Hospital, Karachi) (171-191/Corr.)<br>**xxiii.** 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:<br>iv. Copy of DML of Guangzhou RiboBio Co., Ltd., China is attached<br>v. Batch Certificate for Investigational Product issued by manufacturer is attached.<br>* GMP Certificate of IMP manufacturer is not provided.<br>** 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<br>750 Subjects in Control Group<br>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<br>Batch Certificate for Investigational Product issued by manufacturer is attached.<br>* GMP Certificate of IMP manufacturer is not provided.<br>** 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:

v. 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.

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**AGENDA ITEM XXXII:**

**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 ®<br>Inhaled Novaferon, given 20 µg BID, daily for 7 days | **Biological:** Novaferon ®<br>(a novel recombinant antiviral protein drug)<br>Recombinant Cytokine Gene Derived Protein |
| **Placebo Comparator:** Placebo<br>Inhaled saline (placebo), given BID, daily for 7 days | **Biological:** Placebo (Saline) |

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

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

**G. Placebo:** Saline
**Dosage Form:** Aerosol

**Route:** Inhalation.

**H. 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<br>* 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<br>Protocol No. CRO-009-NOV-(JH509)-2022/Protocol/1.1<br>Version 1.1, dated 09th November, 2022<br><br>* 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<br>* Details regarding Insurance firm/MoU need to be provided |
| 6 | List of participating countries | Hong Kong, China & Pakistan.<br>* 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:<br>iii. Novaferon® (7104 Vials)<br>iv. Placebo (7104 Vials) |
| 9 | Site of the trial | v. Dow University Hospital, Karachi.<br>vi. The Indus Hospital & Health Network, Karachi.<br>vii. 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.<br>**xxiv.** 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:<br>• Copy of GMP Certificate M/s Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan District, Qingdao, Shandong Province, China.<br>• Copy of CoPP for Novaferon® (Recombinant cytokine gene derived protein injection) 10µg/1.0ml/vial, is attached.<br>* 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<br>* 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)<br>* 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.<br>Copy of translation & New Drug Certificate issued by China Food & Drug Administration.<br>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 inspected and certified by Health Canada (see Appendix-4) | 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. |
| 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 | Previously it was informed in the application that, the trial will be carried out 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. | Hong Kong, China & Pakistan.<br>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.<br>M/s CBSCR-ICCBS, University of Karachi<br>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:**<br>*a. Is subject trial the same, which is enlisted on U.S. Trial Registry?*<br>*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.*<br>*c. Is there any connection between M/s Genova Inc., Japan & M/s* | a. Yes, it is the same trial and was registered in us Trial Registry<br><br>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 should be considered as Sponsor as well.<br><br>c. Genova Biotech (Qingdao) co., Ltd is the wholly owned subsidiary of Genova Inc. | 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, |

| | | | |
|---|---|---|---|
| | *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.*<br>*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.* | 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. | 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.<br><br>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.<br><br>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.*

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**AGENDA ITEM XXXIII:**

**APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "FINDING TREATMENTS FOR COVID-19: A PHASE-II, MULTI-CENTRE, ADAPTIVE PLATFORM TRIAL TO ASSESS ANTIVIRAL PHARMACODYNAMICS IN EARLY SYMPTOMATIC COVID-19 (PLATCOV)", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-18/2022-PS (CT)**

Application was submitted by Dr. Muhammad Asim Beg (CNIC: 42201-0543067-7), Principal Investigator PLATCOV Study, Professor and Consultant Parasitologist, Institutional Lead for APMEN, Former Chair Hospital Ethics Committee, Department of Pathology & Microbiology, Aga Khan University Hospital, Stadium Road, Karachi dated 15th September, 2022, wherein request has been made for approval of subject Phase-II Clinical Trial, which will be carried out at Aga Khan University Hospital, Karachi. Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide challan no. 374049140, dated 24th August, 2022. The trial is also enlisted on U.S National Trial Registry with identification number ***NCT05041907*** (https://www.clinicaltrials.gov/ct2/show/NCT05041907)

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

i. **Sponsor/Responsible Party:** University of Oxford, UK.

ii. **Funded by:** Wellcome Trust Grant ref :223195/Z/21/Z through the COVID-19 Therapeutics Accelerator.

iii. **Contact information:** William Schilling, MD +662 203 6333 william@tropmedres.ac
Prof. Nicholas J White, +662 203 6333 nickw@tropmedres.ac

iv. **Brief Summary:**

The trial will develop and validate a platform for quantitative assessment of antiviral effects in low-risk patients with high viral burdens and uncomplicated
COVID-19 to determine in-vivo antiviral activity. In this randomized open label, controlled, group sequential adaptive platform trial, we will assess the performance of three distinct types of intervention relative to control (no treatment):

A: Newly available and repurposed potential antiviral drugs;
B: Positive control: monoclonal antibodies initially but subsequently any therapeutic that is shown to accelerate the rate of viral clearance C: Novel small molecule drugs that have gone through phase 1 testing
PLATCOV study is supported by the Wellcome Trust Grant ref: 223195/Z/21/Z through the COVID-19 Therapeutics Accelerator.

v. **Study Description:**

| **Condition or Disease** | **Intervention/Treatment** | **Phase** |
|---|---|---|
| COVID-19 | 1. Favipiravir (200 mg tablet) (Trade Name: FAVUZA)<br>2. Nitazoxanide (500 mg tablet) (Trade Name: IZATO)<br>3. Molnupravir (200 mg Capsule) (Trade Name: MONUVIR)<br>4. Nirmatrevir/ritonavir (Nirmatrevir 150 mg tablet; Ritonavir: 100 mg tablet) (Trade Name: PAXOVIR)<br>5. Fluoxetine (20 mg tablet) (Trade Name: FLUX)<br>6. Ensitrelvir (Each tablet contains Ensitrelvir fumaric acid 125 mg).<br>7. B REGN-COV2 (600 mg Casirivimab/600 mg Imdevimab)<br>8. Sotrovimab (500 mg /8 ml)<br>9. A combination of Molnupiravir and Nirmatrevir/ritonavir (Trade Name: MONUVIR and PAXOVIR)<br>L0. Evusheld (150 mg of the tixagevimab and 150 mg of the Cligavimab) | Phase-II |

vi. **Arms & Interventions:**

| Arms | Intervention/treatment |
|---|---|
| Active Comparator: Positive control (monoclonals) | Drug: Monoclonal antibodies<br>Monoclonal antibodies: 600mg casirivimab/ 600mg imdevimab given once on D0 |
| Experimental: Favipiravir | Drug: Favipiravir<br>Favipiravir 1800mg BD D0 and 800mg BD for a further 6/7. |
| Experimental: Ivermectin [This arm is now closed to recruitment] | Drug: Ivermectin<br>Ivermectin 600micrograms/kg/day for 7/7. |
| Experimental: Remdesivir [This arm is now closed to recruitment] | Drug: Remdesivir<br>Remdesivir 200mg D0 and 100mg for a further 4/7. |
| Negative control group | Other: No treatment<br>No treatment (except antipyretics- paracetamol) |
| Experimental: Fluoxetine | Drug: Fluoxetine<br>Fluoxetine 40mg OD for 7/7 |
| Experimental: Molnupiravir | Drug: Molnupiravir<br>Molnupiravir 800mg BD for 5/7 |
| Experimental: Nirmatrelvir/ritonavir (e.g. PAXLOVID™) | Drug: Nirmatrelvir/ritonavir (e.g. PAXLOVID™)<br>Nirmatrelvir 300mg BD for 5/7 Ritonavir 100mg BD for 5/7 |
| Experimental: Nitazoxanide | Drug: Nitazoxanide<br>Nitazoxanide 1.5g BD 7/7 |

vii. **Purpose of trial:** The purpose of this study is to evaluate, Quantitative evidence of antiviral activity in patients with COVID-19 is required to justify phase III clinical trials of putative antivirals

There are many potential therapeutics for COVID- 19 and a much larger number of vaccines are in development. Vaccines are the solution but there are concerns over incomplete protection, vaccine hesitancy and waning protective effects over time. Many people over the next 2-3 years will get COVID-19 with substantial morbidity and hundreds of thousands of deaths. For all these reasons effective therapeutics are needed urgently. There is no optimised or validated approach to assess rapidly potential antiviral therapeutics in COVID-19. Drugs are currently selected for clinical study based on activity in cell culture systems (in-vitro) and animal models in-vivo. Unfortunately, the animal models are not sufficiently good to be included in the drug development critical pathway. In order to identity effective antivirals and optimise their dosing. phase 3 studies must be designed appropriately. and progress is as rapid as possible, in vivo antiviral effects must be characterized adequately. This can be achieved in natural COVID-19 infections at an early stage of the disease using the following design.

The proposed trial will develop and validate a platform for quantitative assessment of antiviral effects in low-risk patients with high viral burdens and uncomplicated COVID- 19.

In this randomised open label. controlled. group sequential adaptive platform trial. we will assess the performance of three distinct types of intervention relative to control (no treatment):

A: Newly available and repurposed antiviral drugs; and if available:
B: "Positive control" (e.g., monoclonal antibodies); and later:
C: Small molecule drugs that pass phase 1 testing.

viii. **Trial Monitoring:**

There will be no designated monitor or clinical research associate, however sponsor will do central monitoring of the data entered in defined software. Moreover, an independent Data Safety and Monitoring Board (DSMB) will be set up consisting of qualified volunteers with the necessary knowledge of clinical trials. The DSMB will receive summary reports from MORU as defined per charter or per ad-hoc request, prior to each meeting. An interim report will be prepared by the Trial Statistician for the pre-specified interim analysis. In case of safety concerns, additional information or formal interim analyses can be requested by the DSMB.

The DSMB will meet formally at the following time points:

- Before the study starts
- After the first 50 patients have been accrued into the study (10 per arm)
- At additional time-points as indicated by the DSMB after their review, if deemed necessary.

All DSMB recommendations will be communicated to site PIs. The site PI will be responsible for submitting the written DSMB summary reports with recommendations as applicable to local/national ethics committees and other applicable groups.

ix. **Number of subjects to be recruited:** **1500** Subjects (Globally)

x. **Anticipated cost of the project: Not provided**

xi. **Study design & details:**

| | |
|---|---|
| **Study Type :** | Interventional (Clinical Trial) |
| **Estimated Enrollment :** | **1500** participants (Globally) **250** Subjects from Pakistan. |
| **Allocation:** | Randomized |
| **Intervention Model:** | Parallel Assignment |
| **Masking:** | None (Open label) |
| **Primary Purpose:** | Treatment |
| **Official Title:** | Finding Treatments for COVID-19: A Phase 2 Multi-centre Adaptive Platform Trial to Assess Antiviral Pharmacodynamics in Early Symptomatic COVID-19 (PLATCOV) |
| **Estimated Study Start Date :** | 30th September, 20212 |

| | |
|---|---|
| **Estimated Primary Completion Date :** | August, 2024 |
| **Estimated Study Completion Date :** | August, 2024 |

03. The study carried out under the supervision of Dr. Muhammad Asim Beg (PI). The trial comprises of following objective(s);

**Primary Outcome Measures:**

i. Rate of viral clearance for newly available and repurposed drugs [ Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for each newly available and repurposed drug compared with the no antiviral treatment control i.e. those not receiving study drug

ii. Rate of viral clearance for positive controls (e.g. monoclonal antibodies) [ Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for positive controls (e.g. monoclonal antibodies) compared with the no antiviral treatment control i.e. those not receiving study drug

iii. Rate of viral clearance for small novel molecule drugs [ Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for small novel molecule drugs compared with the no antiviral treatment control i.e. those not receiving study drug

**Secondary Outcome Measures:**

i. Viral kinetic levels in early COVID-19 disease [ Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for each therapeutic arm compared with the no antiviral treatment control i.e. those not receiving study drug

ii. Number of antiviral treatment arms that are shown to be effective i.e. a positive signal (>90% probability of >12.5% acceleration in viral clearance) [ Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for each therapeutic arm compared with the no antiviral treatment control i.e. those not receiving study drug

iii. Rates of viral clearance by treatment arm, as compared against REGN-COV2 (monoclonal antibody cocktail) monoclonal antibody cocktail) or other licensed and available therapeutics with evidence of accelerated viral clearance (monoclonal antibody cocktail) [ Time Frame: Days 0-7]
Rate of viral clearance- estimated from the log10 viral density derived from qPCR of standardised duplicate oropharyngeal swabs/ saliva taken daily from baseline (day 0) to day 7 for each therapeutic arm compared with positive control (e.g. REGN-COV-2 a monoclonal antibody cocktail) or other licensed and available therapeutics with evidence of accelerated viral clearance.

**Other Outcome Measures:**

i. Rates of hospitalisation by treatment arm (hospitalisation for clinical reasons) [ Time Frame: Days 0-28]
Number of hospitalisations up to Day 28 in a treatment arm with an increased rate of viral clearance compared with the negative control i.e. patients not receiving study drug.

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

| S. No. | Document | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-II | Attached |
| 2 | Prescribed processing fee | Rs. 200,000/- deposited vide challan no. 374049140, dated 24th August, 2022 |

| | | |
|---|---|---|
| 3 | Investigator Brochure (s) | **PIL** of following approved products IMPs are attached:<br>**i.** Paxovir (Nirmatrevir 150 mg & Ritonavir: 100 mg) Tablets (17/Corr.)<br>**ii.** Monuvir (Molnupravir) Capsules Mfg:by ESKYEF Pharma Bangladesh (18/Corr.).<br>**iii.** FAVUZA (Favipiravir 200 mg) Mfg:by Sami Pharma, Pakistan (19/Corr.)<br>**iv.** Izato (Nitazoxanide) 500 mg tablet Mfg:by Sami Pharma, Pakistan (21/Corr.)<br>**v.** Flux (Fluoxetine 20 mg tablet) Mfg: By Hilton Pharma, Pakistan. (22-23/Corr.)<br>**vi.** Xocova (Ensitrelvir fumaric acid 125 mg) Tablets Mfg: By Shionogi & Co., Ltd. Japan (24-30/Corr.)<br>**vii.** Xevudy (Sotrovimab) 500 mg /8 ml concentrated solution for infusion Mfg: By GlaxoSmithKline, UK (208-217/Corr.)<br>**Investigators Brochure** of following IMPs is attached:<br>i. S-217622, Mfg: By Shionogi Inc., USA. (31-207/Corr.)<br><br>* IB/PIL of following IMPs are not provided.<br>i. Hydroxychloroquine<br>ii. Remdesivir<br>iii. Lopinavir/Ritonavir<br>iv. Miglustat<br>v. Ivermectin<br>vi. REGN-COV2 with Casirivimab & Imdevimab)<br>vii. Nebulized Unfractionated Heparin<br>viii. Fluvoxamine<br>ix. AZD7442 (Evusheld)<br>** Clarification required that, why different origin IMPs are utilized in a MRCT.<br>*** There is a difference between IMPs mentioned on US Trial registry, Trial protocol & IMPs used in Pakistan for a same study. Clarification required. |
| 4 | Final protocol | Attached<br>Protocol No. VIR21001<br>Version 0.3, dated 23rd August, 2022 |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached. |
| 6 | List of participating countries | Thailand, Brazil, Laos & Pakistan.<br><br>* Some are unconfirmed sites. |
| 7 | Phase of trial. | Phase – II<br>* As the site has no Bioanalytical facilities, so clarification regarding PK/PD Assay need to be submitted that, where theses assay/tests will be conducted |
| 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 approximate required quantity of each IMPs will be as follows:<br>i. FAVUZA (Favipiravir 200 mg tablet) Total 3960 Tablets<br>ii. IZATO (Nitazoxanide 500 mg tablet) Total 2520 tablets<br>iii. MONUVIR (Molnupravir 200 mg Capsule) Total 2400 capsules |

| | | |
|---|---|---|
| | | iv. Nirmatrevir/ritonavir (Nirmatrevir: 150 mg tablet; Ritonavir: 100 mg tablet)<br>a. Nirmatrevir: Total 1200 tablets<br>b. Ritonavir: Total 600 tablets<br>v. Fluoxetine (20 mg Flux tablet) Total 840 Tablets<br>vi. Ensitrelvir (Each tablet contains Ensitrelvir fumaric acid 125 mg) Total 420 Tablets<br>vii. B REGN-COV2 (600 mg Casirivimab/600 mg Imdevimab) Total 60 vials<br>viii. Sotrovimab (500 mg/8 ml) Total 60 vials<br>ix. A combination of Molnupiravir and Nirmatrevir/ritonavir<br>a. Molnupiravir: Total 2400 tablets<br>b. Nirmatrevir: Total 1200<br>c. Ritonavir: Total 600 tablets<br>x. Evusheld (150 mg of the tixagevimab and 150 mg of the Cligavimab) Total 120 vials |
| 9 | Site of the trial | M/s Aga Khan University Hospital, Karachi.<br>* As the site has no Bioanalytical facilities, so clarification regarding PK/PD Assay need to be submitted that, where theses assay/tests will be conducted |
| 10 | Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members. | AKUH IRB/ERC approval, dated 05th August, 2022 for a period of **one year** (w.e.f.05-Aug-2022) is attached. Amendment letter issued on 09th September, 2022 is also attached. |
| 11 | Approval of National Bio-ethics Committee (NBC) | Approval reference letter No. 4-87/COVID-111/22/123, dated 10th August, 2022 (for a period of **Six** months). Approval of amendment reference letter No. 4-87/COVID-111/22/331, dated 15th September, 2022 (for a period of **Six** months) is also attached. |
| 12 | CV's of the Investigators | CVs of following experts are attached.<br>**i.** Dr. Muhammad Asim Beg (PI) (AKUH)(308-337/Corr.)<br>**ii.** Dr. Farah Naz Qamar (Co-PI) (400-412/Corr.)<br>**iii.** Dr. Abdul Momin Kazi (Co-PI) (358-383/Corr.)<br>**iv.** Dr. Syed Faisal Mahmood (Co-Investigator) (338-347/Corr.)<br>**v.** Dr. Najia Bano Ghanchi (Ph.D. Biotechnology) (Co-Investigator) (384-398/Corr.)<br>**vi.** Dr. Aisha Ilyas (Co-Investigator) (414-416/Corr.)<br>**vii.** Dr. Junaid Iqbal (Ph.D. Microbiology) (Co-Investigator) (348-357/Corr.) |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | GMP Certificate(s) of following manufacturer(s) are attached:<br>i. M/s SAMI Pharmaceuticals (Pvt.) Ltd., Karachi.<br>ii. M/s ESKAYEF Pharmaceuticals Ltd., Gazipur, Bangladesh<br>iii. M/s Hilton Pharma (Pvt.) Ltd., Karachi.<br>iv. M/s Shionogi Pharma Co., Ltd., Osaka, Japan (For S-217622 IMPs)<br>CoPP/ Registration Certificates of following manufacturer(s) are provided:<br>v. FAVUZA (Favipiravir 200mg) Tablets. |

| | | |
|---|---|---|
| | | vi. IZATO (Nitazoxanide 500mg) Tablets.<br>vii. MONUVIR (Molnupravir 200 mg) Capsule (CoPP for Ukraine is attached)<br>viii. PAXOVIR (Nirmatrevir150 mg) tablet (CoPP for Ukraine is attached)<br>ix. FLUX (Fluoxetine 20 mg) Total 840 Tablets (Registration letter of FLUX 20mg Capsules is attached instead of Tablets)<br>x. B REGN-COV2 (600 mg Casirivimab/600 mg Imdevimab) Total 60 vials (CoPP attached for 300mg+300mg single dose vial instead of 600+600mg)<br>COA is attached for following:<br>xi. S-217622 IMPs<br><br>GMP Certificate of following are not provided:<br>i. M/s Roche Registration GmbH, Germany.<br>ii. M/s GENENTECH Inc., Hillsboro, Oregon, USA.<br>iii. Manufacturer of Ritonavir 100mg tablet<br>iv. Manufacturer of Ensitrelvir fumaric acid 125 mg<br>v. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion<br>vi. Any other manufacturer whom IMPs details not attached with dossier.<br><br>CoPP of the following are not provided:<br>i. Ritonavir 100mg tablet<br>ii. Ensitrelvir fumaric acid 125 mg<br>iii. Sotrovimab (500 mg/8 ml) Infusion<br>iv. Evusheld Tixagevimab 150mg & Cligavimab 150mg)<br>v. CoPP of other IMPs, which is not included in the list with dossier. |
| 14 | Pre-clinical/clinical safety studies | Attached. |
| 15 | Summary of Protocol | Attached. |
| 16 | Summary of Investigator Brochure | Not provided. |
| 17 | Adverse Event Reporting Form | ADR reporting form as per CIOMS is not provided. |
| 18 | No of patients to be enrolled in each center. | 250 subjects from Pakistan<br>1250 subjects from Brazil, Thailand, Laos & other two countries (Yet unconfirmed)<br>Total 1500 Subjects (Globally). |
| 19 | Name of Monitors & Clinical Research Associate | There will be no designated monitor or clinical research associate, however sponsor will do central monitoring of the data entered in defined software. Moreover, an independent Data Safety and Monitoring Board (DSMB) will be set up consisting of qualified volunteers with the necessary knowledge of clinical trials. |
| 20 | Evidence of registration in country of origin. | Registration Certificates/CoPP of following product(s)/manufacturer(s) are attached:<br>**i.** FAVUZA (Favipiravir 200 mg) Mfg:by Sami Pharma, Pakistan (578 & 583/Corr.)<br>**ii.** Izato (Nitazoxanide) 500 mg tablet Mfg:by Sami Pharma, Pakistan (579/Corr.)<br>**iii.** Monuvir (Molnupravir) Capsules Mfg:by ESKYEF Pharma Bangladesh (587-588/Corr.). |

| | | |
|---|---|---|
| | | **iv.** Flux (Fluoxetine 20 mg tablet) Mfg: By Hilton Pharma, Pakistan. (596-597/Corr.)<br>**v.** Paxovir (Nirmatrevir 150 mg & Ritonavir: 100 mg) Tablets Mfg:by ESKYEF Pharma Bangladesh (602-603/Corr.).<br>**vi.** Ronapreve (Casirivimab/Imdevimab 300mg/300mg) 1 Single Dose Vial + 1 Single Dose Vial, Solution for Injection / Infusion Mfg:by Hoffmann-La Roche Ltd., Switzerland. (617-641/Corr.).<br>* It need to be clarified that, as it is a MRCT so why IMPs from different origin are utilized at different international Clinical trial Site(s) |
| 21 | Copy of registration letter (if registered in Pakistan) | Registration Certificates/CoPP of following product(s)/manufacturer(s) are attached:<br>**i.** FAVUZA (Favipiravir 200 mg) Mfg:by Sami Pharma, Pakistan (578 & 583/Corr.)<br>**ii.** Izato (Nitazoxanide) 500 mg tablet Mfg:by Sami Pharma, Pakistan (579/Corr.)<br>**iii.** Monuvir (Molnupravir) Capsules Mfg:by ESKYEF Pharma Bangladesh (587-588/Corr.).<br>**iv.** Flux (Fluoxetine 20 mg tablet) Mfg: By Hilton Pharma, Pakistan. (596-597/Corr.)<br>* It need to be clarified that, as it is a MRCT so why IMPs from different origin are utilized at different international Clinical trial Site(s) |
| 22 | Sample of label of the investigational product / drug. | Attached. |
| 22 | Duration of trial | Approximately 03 Years & 28 Days for individual patient involvement. |
| 23 | Undertaking on Stamp paper | Attached. |

05. After initial scrutiny following shortcomings are recorded:

i. There is a difference in IMPs mentioned in application, US Trial Registry & in the protocol. Clarification required.
ii. Anticipated cost of the project is not mentioned.
iii. The IMPs (S-217622, Manufactured by Shionogi Inc., USA) is not part of the intervention mentioned in attached protocol. Attached protocol is for AZD7442 (Evusheld). Clarification need to be provided.
iv. Investigator's Brochure / PIL (for registered products) of following IMPs are not provided.

   a. Hydroxychloroquine
   b. Remdesivir
   c. Lopinavir/Ritonavir
   d. Miglustat
   e. Ivermectin
   f. REGN-COV2 with Casirivimab & Imdevimab)
   g. Nebulized Unfractionated Heparin
   h. Fluvoxamine
   i. AZD7442 (Evusheld)

v. Clarification required that, why different origin IMPs are utilized in a Multi-Regional Clinical Trial (MRCT).
vi. There is a difference between IMPs mentioned on US Trial registry, Trial protocol & IMPs used in Pakistan for a same study. Clarification required.
vii. Proposed Clinical Trial Site has no Bioanalytical facilities, so clarification regarding PK/PD Assay (as required in Phase-II CT) need to be submitted that, where theses assay/tests will be conducted.
viii. GMP Certificate of following are not provided:

   a. M/s Roche Registration GmbH, Germany.
   b. M/s GENENTECH Inc., Hillsboro, Oregon, USA.
   c. Manufacturer of Ritonavir 100mg tablet

d. Manufacturer of Ensitrelvir fumaric acid 125 mg
e. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion
f. Any other manufacturer whom IMPs details not attached with dossier.

ix. CoPP of the following are not provided:

a. Ritonavir 100mg tablet
b. Ensitrelvir fumaric acid 125 mg
c. Sotrovimab (500 mg/8 ml) Infusion
d. Evusheld Tixagevimab 150mg & Cligavimab 150mg)
e. CoPP of other IMPs, which is not included in the list with dossier.

x. ADR reporting form as per CIOMS is not provided.
xi. It need to be clarified that, as it is a MRCT so why IMPs from different origin are utilized at different international Clinical Trial Site(s).

06. In the view of above, shortcomings communicated vide letter bearing even number dated 12th October, 2022, response is awaited.

07. It is submitted that, the case was presented before CSC in its 35th meeting, held on 13th October, 2022. Further, Dr. Muhammad Asim Beg (PI) (who joined the meeting through Zoom) responded to the questions raised the expert members, Prof. Munawar Alam Ansari & Prof. Fazal Subhan, regarding the title & scope of the trial with respect to the term "Pharmacodynamics".

08. As a result, the Committee of Experts advised the PI for revision of trial subject & its scope in regard to "Pharmacodynamics", as it's a very broad term & need to be more specific.\

09. After detailed deliberations & discussion, the Committee decided the case as under:

**Decision:**

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

i. There is a difference in IMPs mentioned in application, US Trial Registry & in the protocol. Clarification required.
ii. Anticipated cost of the project is not mentioned.
iii. The IMPs (S-217622, Manufactured by Shionogi Inc., USA) is not part of the intervention mentioned in attached protocol. Attached protocol is for AZD7442 (Evusheld). Clarification need to be provided.
iv. Investigator's Brochure / PIL (for registered products) of following IMPs are not provided.

a. Hydroxychloroquine
b. Remdesivir
c. Lopinavir/Ritonavir
d. Miglustat
e. Ivermectin
f. REGN-COV2 with Casirivimab & Imdevimab)
g. Nebulized Unfractionated Heparin
h. Fluvoxamine
i. AZD7442 (Evusheld)

v. Clarification required that, why different origin IMPs are utilized in a Multi-Regional Clinical Trial (MRCT).
vi. There is a difference between IMPs mentioned on US Trial registry, Trial protocol & IMPs used in Pakistan for the same study. Clarification is therefore required.
vii. Proposed Clinical Trial Site has no Bioanalytical facilities, so clarification regarding PK/PD Assay (as required in Phase-II CT) need to be submitted that, where theses assay/tests will be conducted.
viii. GMP Certificate of following are not provided:

a. M/s Roche Registration GmbH, Germany.
b. M/s GENENTECH Inc., Hillsboro, Oregon, USA.
c. Manufacturer of Ritonavir 100mg tablet
d. Manufacturer of Ensitrelvir fumaric acid 125 mg

e. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion
f. Any other manufacturer whom IMPs details not attached with dossier.

ix. CoPP of the following are not provided:

f. Ritonavir 100mg tablet
g. Ensitrelvir fumaric acid 125 mg
h. Sotrovimab (500 mg/8 ml) Infusion
i. Evusheld Tixagevimab 150mg & Cligavimab 150mg)
j. CoPP of other IMPs, which is not included in the list with dossier.

x. ADR reporting form as per CIOMS is not provided.
xi. It need to be clarified that, as it is a MRCT so why IMPs from different origin are utilized at different international Clinical Trial Site(s).

The applicant is directed to reply within 30 days positively.

10. Accordingly, CSC decision was communicated to the applicant/PI on 14th October, 2022. Dr. Muhammad Asim Beg, Principal Investigator PLATCOV Clinical Trial, submitted reply in reference to CSC decision, on 27th October, 2022.

11. Summary of submitted reply along with attachments & remarks by the Division is as follows:

| Sr. | Descriptions / Shortcomings | Reply | Remarks |
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| 01 | There is a difference in IMPs mentioned in application, US Trial Registry & in the protocol. Clarification required. | Thank you for your comments. Please see below for a longer explanation but in brief, the IMPs mentioned in the application match those which we have indicated we will assess in the protocol. The US Trial Registry reflects the drugs we are currently assessing in Thailand and Brazil and will be updated prior to the study start in Pakistan, to reflect the drugs we will assess there, and are assessing in other countries.<br>PLATCOV is a multicentre, adaptive platform trial that aims to determine the clinical antiviral efficacy of a number of therapeutics against COVID-19, to determine if they are effective antivirals or not, and help inform Phase III studies and healthcare decisions regarding the procurement and use of therapeutics. Due to the platform nature of the study, we have included in the protocol some drugs which we are not currently assessing. Although these therapeutics are named in the protocol and have appendices, we make clear that we are only requesting permission to use the following drugs in Pakistan- favipiravir, fluoxetine, Nitazoxanide, Molnupiravir, Nirmatrelvir/ritonavir, Ensitrelvir, and a combination of Molnupiravir and Nirmatrelvir/ritonavir, REGN-COV2 Sotrovimab and Evusheld.<br>These drugs are the same as the ones we have provided documents for. Of note, Ensitrelvir is also known as S-217622 and this is referenced in the Ensitrelvir appendix.<br>The US trial Registry Clintrials.gov contains all the drugs which we are currently assessing or have assessed in Thailand and Brazil. We | It is informed that, only following IMPs will be utilized in the trial:<br>a) Favipiravir<br>b) Fluoxetine,<br>c) Nitazoxanide<br>d) Molnupiravir<br>e) Nirmatrelvir/ritonavir, Ensitrelvir<br>f) A combination of Molnupiravir and Nirmatrelvir/Ritonavir, REGN-COV2 Sotrovimab and Evusheld. |

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| | | assessed the efficacy of Ivermectin and found that it was not effective, and this arm was stopped. In addition, the Remdesivir arm was stopped, as we demonstrated that this drug accelerated viral clearance by about 40%. We are continually updating Clintrials.gov to reflect the medications being used in the sites of the study and will add new interventions prior to evaluating them. In addition, we indicate therapeutics which have been successfully evaluated (e.g. Ivermectin and Remdesivir), but make it clear that these are no longer being used. | |
| 02 | Anticipated cost of the project is not mentioned. | The anticipated Cost of the project is 906078 GBP | --- |
| 03 | The IMPs (S-217622, Manufactured by Shionogi Inc., USA) is not part of the intervention mentioned in attached protocol. Attached protocol is for AZD7442 (Evusheld). Clarification need to be provided. | Thank you again and apologies for any confusion caused. S-217622 is Ensitrelvir which is mentioned in the protocol, S-217622 being the name used in earlier drug development. That this drug is designated by both names is mentioned in the Ensitrelvir appendix. | --- |
| 04 | Investigator's Brochure / PIL (for registered products) of following IMPs are not provided.<br>a. Hydroxychloroquine<br>b. Remdesivir<br>c. Lopinavir/Ritonavir<br>d. Miglustat<br>e. Ivermectin<br>f. REGN-COV2 with Casirivimab & Imdevimab)<br>g. Nebulized Unfractionated Heparin<br>h. Fluvoxamine<br>i. AZD7442 (Evusheld) | a) Hydroxychloroquine (Not part of Pakistan Protocol)<br>b) Remdesivir (Not part of Pakistan Protocol)<br>c) Lopinavir/Ritonavir (Not part of Pakistan Protocol)<br>d) Miglustat (Not part of Pakistan Protocol)<br>e) Ivermectin (Not part of Pakistan Protocol)<br>f) Nebulized Unfractionated Heparin (Not part of Pakistan Protocol)<br>g) Fluvoxamine (Not part of Pakistan Protocol)<br>h) REGN-COV2 with Casirivimab and Imdevimab, Thank you. We have attached the Patient Information Sheet.<br>i) AZD7442 (Evusheld). Already shared with the initial application (Refer to the initial application dated 15/09/2022) | It is informed that, attached protocol with reply is specifically for AKUH with reference to protocol number: PLATCOV_Protocol (for AKU) _V0.3 dated 23 Aug 22 (Based on master protocol_V.2.0 dated 06 Jul 21 and FTM EC 6.0 MASTER).<br>And following IMPs are part of the trial, so, any clarification/justification from sponsor & revised protocol for Pakistan only need to be provided:<br>a. Hydroxychloroquine<br>b. Remdesivir<br>c. Lopinavir/Ritonavir<br>d. Miglustat<br>e. Ivermectin<br>f. Nitazoxanide<br>g. REGN-COV2 |

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| | | | h. Nebulized Unfractionated Heparin<br>i. Favipiravir<br>j. Molnupiravir<br>k. Nirmatrelvir/Ritonavir (e.g. PAXLOVID™)<br>l. Sotrovimab<br>m. Fluoxetine<br>n. Fluvoxamine<br>o. AZD7442 (Evusheld)<br>p. Ensitrelvir |
| 05 | Clarification required that, why different origin IMPs are utilized in a Multi-Regional Clinical Trial (MRCT). | Thank you. Some drugs have already been assessed in patients in Brazil and Thailand (e.g. Ivermectin and Remdesivir) and so these have been removed from the study. Ideally, we would assess all medications in all countries at the same time, although practically this has not proved possible because some drugs are not easily available in all countries, and regulatory approvals have different schedules. For instance, the monoclonal antibodies and newer COVID-19 antiviral drugs (e.g. Pfizer's Paxlovid), have been sold to governmental health organizations and are not able to be purchased for study use, despite numerous requests to the pharmaceutical companies. As a result, to give an example, we were only able to assess casirivimab/imdevimab (REGN-COV2) in Thailand, as it was not possible to acquire in Brazil. These reasons explain. The discrepancies between countries, although these are small. The IMPs for which we are requesting permission to use are those that are being used (e.g. Favipiravir Fluoxetine, Nitazoxanide, Molnupiravir, Nirmatrelvir/Ritonavir, (REGNCOV-2) or we aim will all be concurrently assessed in Thailand and Brazil (e.g. Ensitrelvir, a combination of Molnupiravir and Nirmatrelvir / ritonavir, Sotrovimab and Evusheld). | It is requested if some of the IMPs already assessed & are removed from the study (as informed in reply), so, revised/amended protocol specifically for Pakistan need to be provided with IRB & NBC approvals. |
| 06 | There is a difference between IMPs mentioned on US Trial registry, Trial protocol & IMPs used in Pakistan for a same study. Clarification required. | Thank you please see answer to question 1 and 5 above. | --- |
| 07 | Proposed Clinical Trial Site has no Bioanalytical facilities, so clarification regarding PK/PD Assay (as required in Phase-II CT) need to be | Thank you, the samples for PK/PD may be transferred to Mahidol Oxford Tropical Medicine Research Unit (MORU) or other designated testing facilities outside the site country, with appropriate material transfer agreements (MTA) and associated approvals prior to shipment. (Refer to page 21 section 7.9 of protocol) | Material Transfer Agreement with Mahidol Oxford Tropical Medicine Research Unit (MORU) or other designated Bio-Analytical Laboratory |

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| | submitted that, where theses assay/tests will be conducted. | | along with SOPs for PK/PD sampling & its shipment, needs to be provided as described in the protocol section 7.9 of protocol |
| 08 | GMP Certificate of following are not provided:<br>a. M/s Roche Registration GmbH, Germany.<br>b. M/s GENENTECH Inc., Hillsboro, Oregon, USA.<br>c. Manufacturer of Ritonavir 100mg tablet<br>d. Manufacturer of Ensitrelvir fumaric acid 125 mg<br>e. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion<br>f. Any other manufacturer whom IMPs details not attached with dossier. | a) M/s Roche Registration GmbH Germany. (The medication will not be procured from this pharmaceutical)<br>b) M/s GENETECH Inc. Hillsboro, Oregon, USA (GMP Shared)<br>c) Manufacturer of Ritonavir 100mg tablet (GMP shared)<br>d) Manufacturer of Ensitrelvir fumaric acid 125mg (GMP Shared)<br>e) GlaxoSmithKline, UK manufacturer of Sotrovimab (500mg /8 ml) infusion<br>f) Any other manufacturer whose IMPs details are not attached with dossier<br>We have been in discussion with GlaxoSmithKline regarding the purchase of Sotrovimab for our study and for documents which would be required for this regulatory submission. At present, we have not been able to get a GMP certificate. We will continue to try to attain this. In the meantime, we will not use this medication, and when we acquire this document, and any others required, we will submit these to you for your approval, prior to use of this medication, but given the pandemic context would not want this to delay the approval of the rest of the IMPs. | GMP Certificate(s) are mandatory requirement under the Bio-Study Rules, 2017. So, it is therefore again requested to provide GMP Certificate(s) of following manufacturer(s):<br>i. Manufacturer of Ensitrelvir fumaric acid 125 mg<br>ii. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion<br>iii. Any other manufacturer whom IMPs details not attached with dossier. |
| 09 | CoPP of the following are not provided:<br>a. Ritonavir 100mg tablet<br>b. Ensitrelvir fumaric acid 125 mg<br>c. Sotrovimab (500 mg/8 ml) Infusion<br>d. Evusheld Tixagevimab 150mg & Cligavimab 150mg)<br>e. CoPP of other IMPs, which is not included in the list with dossier. | a) Ritonavir 100mg tablet, The CoPP is shared as it is a combination medication or Nirmatrelvir/ Ritonavir<br>b) Ensitrelvir fumaric acid 125mg, Certificate of Analysis is provided.<br>c) Sotrovimab (500mg /8 ml) infusion<br>d) Evusheld Tixagevimab 150 mg & Cligavimab 150mg<br>e) CoPP of other IMPs Which is not included in the list with dossier<br>Thank you. We have been unable to get the CoPP for both Sotrovimab and Evusheld. We will continue to try and get these. In the meantime, we will not use this medication, and when we acquire this document, and any others required, we will submit these to you for your approval, prior to use of this medication, but given the pandemic context would not want this to delay the approval of the rest of the IMPs. | CoA are not replacement of CoPP as CoPP is a mandatory requirement under the Bio-Study Rules, 2017. It is therefore again requested to provide CoPP for following products:<br>i. Ensitrelvir fumaric acid 125 mg<br>ii. Sotrovimab (500 mg/8 ml) Infusion<br>iii. Evusheld Tixagevimab 150mg & Cligavimab 150mg)<br>iv. CoPP of other IMPs as mentioned in the protocol, which are not included in the list with dossier need to be provided. |

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| 10 | ADR reporting form as per CIOMS is not provided. | The protocol requires that the PLATCOV safety team inform the Data Safety and Management Board if Serious Adverse Events occur, and these be relayed to local ECs/ regulatory authorities. In addition, adverse events of are also recorded in the CRF, and causality ascribed. All SUSARs will be reported by the site PI to the relevant Competent<br>Authority and to the local Ethics Committee and other parties as applicable.<br>The protocol does not mention ADR reporting as per CIOM, but reporting should occur as per local ethical and regulatory guidance. If this is required by DRAP we will comply, but we believe the reporting of adverse reactions through the above-described mechanisms (SAEs and SUSARs) given the widespread use of these medications, their good safety profiles (which are all registered in countries around-the world, except Ensitrelvir) and the context of the COVID-1g-pandemic are appropriate. For drugs that are pre-registration we will be registered to report ADRs to. the drug company as per CIOM. | --- |
| 11 | It need to be clarified that, as it is a MRCT so why IMPs from different origin are utilized at different international Clinical Trial Site(s). | Thank you. Ideally we would use the same branded formulation of each drug at all sites. However, for repurposed drugs where there are available high-quality generics locally in countries, we have opted for the option of using locally available IMPs. The reasons are speed of use of medications in this platform trial (where arms are dropped and added regularly) thus limiting delays with import because these generics abide to high standards and quality of manufacturing overseen, by the country's regulatory authority, and are what is available currently to people living in that country during the pandemic (should a drug be shown to be effective). For some new COVID-19 drugs it has also not been possible to use the same medication at different sites, e.g. Pfizer's Paxlovid, which is sold to governmental health agencies and is not available for purchase. The Paxlovid we use in Thailand was donated to the study for sole use in Thailand by the Thai Ministry of Public Health, and is not possible to acquire, or procure to import into Pakistan, and as such we are procuring from Eskayef Bangladesh, a US FDA accredited facility which manufacturers high-quality generics, and one of the leading generics manufacturers globally. This IMP will also be used in Brazil.<br>We assessed both trade-marked and generic Remdesivir in the study and the results were the same, which adds reassurance for those not able to access trade-marked pharmaceuticals in Low- and Middle-Income Countries. Finally, with the drug levels and PK assessments we would be | As per submitted reply regarding use of different origin drugs in a MRCT trial, authorization from Sponsor for use of different origin IMPs need to be provided. |

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| | | able to determine differences related to drugs of different origins in the study. | |

12. After evaluation of the submitted reply following shortcomings observed & still need to be fulfilled:

i. It is informed that, only following IMPs will be utilized in the trial:
   a. Favipiravir
   b. Fluoxetine,
   c. Nitazoxanide
   d. Molnupiravir
   e. Nirmatrelvir/ritonavir, Ensitrelvir
   f. A combination of Molnupiravir and Nirmatrelvir/Ritonavir, REGN-COV2 Sotrovimab and Evusheld.

ii. It is informed that, attached protocol with reply is specifically for AKUH with reference to protocol number: PLATCOV_Protocol (for AKU) _V0.3 dated 23 Aug 22 (Based on master protocol_V.2.0 dated 06 Jul 21 and FTM EC 6.0 MASTER). And following IMPs are part of the trial, so, any clarification/justification from sponsor & revised protocol for Pakistan only need to be provided:
   a. Hydroxychloroquine
   b. Remdesivir
   c. Lopinavir/Ritonavir
   d. Miglustat
   e. Ivermectin
   f. Nitazoxanide
   g. REGN-COV2
   h. Nebulized Unfractionated Heparin
   i. Favipiravir
   j. Molnupiravir
   k. Nirmatrelvir/Ritonavir (e.g. PAXLOVID™)
   l. Sotrovimab
   m. Fluoxetine
   n. Fluvoxamine
   o. AZD7442 (Evusheld)
   p. Ensitrelvir

iii. It is requested if some of the IMPs already assessed & are removed from the study (as informed in reply), so, revised/amended protocol specifically for Pakistan need to be provided with IRB & NBC approvals.

iv. Material Transfer Agreement with Mahidol Oxford Tropical Medicine Research Unit (MORU) or other designated Bio-Analytical Laboratory along with SOPs for PK/PD sampling & its shipment, needs to be provided as described in the protocol section 7.9 of protocol.

v. GMP Certificate(s) are mandatory requirement under the Bio-Study Rules, 2017. So, it is therefore again requested to provide GMP Certificate(s) of following manufacturer(s):
   a. Manufacturer of Ensitrelvir fumaric acid 125 mg
   b. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion
   c. Any other manufacturer whom IMPs details not attached with dossier.

vi. CoA are not replacement of CoPP as CoPP is a mandatory requirement under the Bio-Study Rules, 2017. It is therefore again requested to provide CoPP for following products:
   a. Ensitrelvir fumaric acid 125 mg
   b. Sotrovimab (500 mg/8 ml) Infusion
   c. Evusheld Tixagevimab 150mg & Cligavimab 150mg)
   d. CoPP of other IMPs as mentioned in the protocol, which are not included in the list with dossier need to be provided.

vii. As per submitted reply regarding use of different origin drugs in a MRCT trial, authorization from Sponsor for use of different origin IMPs need to be provided.

13. After approval from Chairman CSC, above mentioned shortcomings communicated to the applicant/PI on 31st October, 2022. Applicant reply communicated electronically on 16th November, 2022. Summary of submitted reply along with remarks by the Division is as follows:
Summary of submitted reply along with attachments is as follows:

| Sr. | Descriptions / Shortcomings | Reply | Remarks |
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| 01 | It is informed that, only following IMPs will be utilized in the trial: | This is correct - we are trying to attain the requisite | Both Sotrovimab and Evusheld are still part of the |

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| | a. Favipiravir<br>b. Fluoxetine,<br>c. Nitazoxanide<br>d. Molnupiravir<br>e. Nirmatrelvir/ritonavir, Ensitrelvir<br>f. A combination of Molnupiravir and Nirmatrelvir/Ritonavir, REGN-COV2 Sotrovimab and Evusheld. | documents for Sotrovimab and Evusheld at the moment but this is proving difficult. It has been indicated that it is not possible to get conditional approval for these drugs while we try and attain the documents, so we have removed them from the protocol. Given the rapidly changing nature of the pandemic, conditional approval would have been our preferred course of action and we would not have used them without written permission from DRAP first. | protocol & requisite documents are not provided yet. It is again informed that, there is no provision of conditional approval under the Bio-Study Rules, 2017. |
| 02 | It is informed that, attached protocol with reply is specifically for AKUH with reference to protocol number: PLATCOV_Protocol (for AKU) _V0.3 dated 23 Aug 22 (Based on master protocol_V.2.0 dated 06 Jul 21 and FTM EC 6.0 MASTER). And following IMPs are part of the trial, so, any clarification/justification from sponsor & revised protocol for Pakistan only need to be provided:<br>a. Hydroxychloroquine<br>b. Remdesivir<br>c. Lopinavir/Ritonavir<br>d. Miglustat<br>e. Ivermectin<br>f. Nitazoxanide<br>g. REGN-COV2<br>h. Nebulized Unfractionated Heparin<br>i. Favipiravir<br>j. Molnupiravir<br>k. Nirmatrelvir/Ritonavir (e.g. PAXLOVID™)<br>l. Sotrovimab<br>m. Fluoxetine<br>n. Fluvoxamine<br>o. AZD7442 (Evusheld)<br>p. Ensitrelvir | Thank you, we have attached the amended protocol that reflects the IMPs that will be used by the AKU Pakistan site. | Following IMPs are mentioned in schedule 16 as follows:<br>16.1 Nitazoxanide<br>16.2 REGN-COV2<br>16.3 Not mentioned.<br>16.4 Not mentioned.<br>16.5 Not mentioned.<br>16.6 Not mentioned.<br>16.7 Not mentioned.<br>16.8 Favipiravir<br>16.9 Molnupiravir<br>16.10 Nirmatrelvir/ritonavir (e.g. PAXLOVID™)<br>16.11 Fluoxetine<br>16.12 Ensitrelvir<br><br>It needs to be clarified that, if the protocol is revised form version 0.2 to 0.3, the IMPs should be in uniform manner/number & remaining drugs need to be excluded from appendix 4 also. |
| 03 | It is requested if some of the IMPs already assessed & are removed from the study (as informed in reply), so, revised/amended protocol specifically for Pakistan need to be provided with IRB & NBC approvals. | We have updated the protocol to reflect the drugs which we currently plan to assess in Pakistan along with IRB and NBC approvals. | AKUH-IRB/ERC approval dated 15th November, 2022 is attached<br>NBC approval Ref: No.4-87/COVID-111/22/608, dated 15th November, 2022 is attached. (for six months) |
| 04 | Material Transfer Agreement with Mahidol Oxford Tropical Medicine Research Unit (MORU) or other designated Bio-Analytical Laboratory | Thank you we have attached the SOPs for PK/PD sampling and Shipment. The need for an MTA with | Un-signed draft MTA for PK/PD Studies between Mahidol Oxford Tropical Medicine Research Unit & |

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| | along with SOPs for PK/PD sampling & its shipment, needs to be provided as described in the protocol section 7.9 of protocol. | the Mahidol Oxford Tropical Medicine Research Unit depends on the study starting successfully as well as individual drugs requiring intense PK-PD, which we cannot know until the drugs have been assessed. We have attached the MTA draft for your reference which is reviewed by both the sponsor and the institution and is in the signing process. | Aga Khan University Hospital, Karachi. |
| 05 | GMP Certificate(s) are mandatory requirement under the Bio-Study Rules, 2017. So, it is therefore again requested to provide GMP Certificate(s) of following manufacturer(s):<br>a. Manufacturer of Ensitrelvir fumaric acid 125 mg<br>b. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion<br>c. Any other manufacturer whom IMPs details not attached with dossier. | We have attached the GMP certificate for Ensitrelvir fumaric acid 125mg. For the other medications, we have removed these from the protocol. | No GMP Certificate is attached with reply dated 16th November, 2022. |
| 06 | CoA are not replacement of CoPP as CoPP is a mandatory requirement under the Bio-Study Rules, 2017. It is therefore again requested to provide CoPP for following products:<br>a. Ensitrelvir fumaric acid 125 mg<br>b. Sotrovimab (500 mg/8 ml) Infusion<br>c. Evusheld Tixagevimab 150mg & Cligavimab 150mg)<br>d. CoPP of other IMPs as mentioned in the protocol, which are not included in the list with dossier need to be provided. | Since the drug is in an investigational phase, CoPP is not available. We have attached CoA instead. For the rest of the IMPs, we have removed them from the protocol. | --- |
| 07 | As per submitted reply regarding use of different origin drugs in a MRCT trial, authorization from Sponsor for use of different origin IMPs need to be provided. | We have attached the authorization letter from the Sponsor. | --- |

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

i. Both Sotrovimab and Evusheld are still part of the protocol & requisite documents are not provided yet. It is again informed that, there is no provision of conditional approval under the Bio-Study Rules, 2017.

ii. Following IMPs are mentioned in schedule 16 as follows:
   a. 16.1 Nitazoxanide.
   b. 16.2 REGN-COV2
   c. 16.3 Not mentioned.
   d. 16.4 Not mentioned.
   e. 16.5 Not mentioned.
   f. 16.6 Not mentioned.
   g. 16.7 Not mentioned.
   h. 16.8 Favipiravir.
   i. 16.9 Molnupiravir.
   j. 16.10 Nirmatrelvir/ritonavir (e.g. PAXLOVID™)
   k. 16.11 Fluoxetine.
   l. 16.12 Ensitrelvir

iii. It needs to be clarified that, if the protocol is revised form version 0.2 to 0.3, the IMPs should be in uniform manner/number & remaining drugs need to be excluded from appendix 4 also.

iv. Un-signed draft MTA for PK/PD Studies between Mahidol Oxford Tropical Medicine Research Unit & Aga Khan University Hospital, Karachi.
v. It is informed that, there is no GMP Certificate attached with reply dated 16th November, 2022. It is again informed that, CoA are not replacement of CoPP as CoPP is a mandatory requirement under the Bio-Study Rules, 2017. It is therefore again requested to provide CoPP for following products:
    a. Ensitrelvir fumaric acid 125 mg.
    b. Sotrovimab (500 mg/8 ml) Infusion
    c. Evusheld Tixagevimab 150mg & Cligavimab 150mg)
vi. CoPP of other IMPs as mentioned in the protocol, which are not included in the list with dossier need to be provided.

15. Case was placed before 36th CSC meeting & the Committee decided the application 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. Both Sotrovimab and Evusheld are still part of the protocol & requisite documents are not provided yet. It is again informed that, there is no provision of conditional approval under the Bio-Study Rules, 2017.
ii. Following IMPs are mentioned in schedule 16 as follows:
    a. 16.1 Nitazoxanide.
    b. 16.2 REGN-COV2
    c. 16.3 Not mentioned.
    d. 16.4 Not mentioned.
    e. 16.5 Not mentioned.
    f. 16.6 Not mentioned.
    g. 16.7 Not mentioned.
    h. 16.8 Favipiravir.
    i. 16.9 Molnupiravir.
    j. 16.10 Nirmatrelvir/ritonavir (e.g. PAXLOVID™)
    k. 16.11 Fluoxetine.
    l. 16.12 Ensitrelvir
iii. It needs to be clarified that, if the protocol is revised form version 0.2 to 0.3, the IMPs should be in uniform manner/number & remaining drugs need to be excluded from appendix 4 also.
iv. Un-signed draft MTA for PK/PD Studies between Mahidol Oxford Tropical Medicine Research Unit & Aga Khan University Hospital, Karachi.
v. It is informed that, there is no GMP Certificate attached with reply dated 16th November, 2022. It is again informed that, CoA are not replacement of CoPP as CoPP is a mandatory requirement under the Bio-Study Rules, 2017. It is therefore again requested to provide CoPP for following products:
    a. Ensitrelvir fumaric acid 125 mg.
    b. Sotrovimab (500 mg/8 ml) Infusion
    c. Evusheld Tixagevimab 150mg & Cligavimab 150mg)
vi. CoPP of other IMPs as mentioned in the protocol, which are not included in the list with dossier need to be provided.

*Further, applicant was given one last opportunity to provide requisite documents within 15 days positively, failing which the application will be liable to be rejected.*

16. Accordingly, CSC decision was communicated vide letter bearing no.16-36/2022 DD(PS), dated 25th November, 2022.

17. Reply in reference to letter bearing no.16-36/2022 DD(PS), dated 25th November, 2022 received from Dr. Muhammad Asim Beg, Principal Investigator PLATCOV Study, Professor and Consultant Parasitologist, Institutional Lead for APMEN, Former Chair Hospital Ethics Committee, Department of Pathology & Microbiology, Aga Khan University Hospital, Stadium Road, Karachi, received on dated 06th December, 2022.

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

| Sr. | Descriptions / Shortcomings | Reply | Remarks |
|---|---|---|---|

| | | | |
|---|---|---|---|
| 01 | Both Sotrovimab and Evusheld are still part of the protocol & requisite documents are not provided yet. It is again informed that, there is no provision of conditional approval under the Bio-Study Rules, 2017 | Sotrovimab and Evusheld are removed from the protocol (Refer to attached protocol version 0.4 Page 7, intervention section) | --- |
| 02 | Following IMPs are mentioned in schedule 16 as follows:<br>16.1 Nitazoxanide<br>16.2 REGN-COV2<br>16.3 Not mentioned.<br>16.4 Not mentioned.<br>16.5 Not mentioned.<br>16.6 Not mentioned.<br>16.7 Not mentioned.<br>16.8 Favipiravir<br>16.9 Molnupiravir<br>16.10 Nirmatrelvir/ritonavir (e.g. PAXLOVID™)<br>16.11 Fluoxetine<br>16.12 Ensitrelvir<br><br>It need to be clarified that, if the protocol revised form version 0.2 to 0.3, so, IMPs should be in uniform manner/number & remaining drugs need to be excluded from appendix 4 also. | IMPs included in the protocol version 0.4 are updated with numbers as follows in schedule 16:<br>a) 16.1Nitazoxanide<br>b) 16.2 REGN-COV2<br>c) 16.3 Favipiravir<br>d) 16.4 Molnupiravir<br>e) 16.5 Nirmatrelvir/ritonavir (Paxlovid)<br>l) 16.6 Fluoxetine<br>g) 16.7 Ensitrelvir<br>The combination of Molnupiravir and Nirmatrelvir/ritonavir is not added to this section because each medication is already mentioned separately. Refer to schedule 16.4 page 44 for details on Molnupiravir as a medication. Information on Nirmatrelvir/Ritonavir can be found on page 46 of Schedule 16.5. | --- |
| 03 | It needs to be clarified that, if the protocol is revised from version 0.2 to 0.3, the IMPs should be in uniform manner/number & remaining drugs need to be excluded from appendix 4 also. | The protocol is revised from version 0.3 to 0.4 instead of 0.2 to 0.3, the IMPs are updated in a uniform manner in appendix 4 as well. (Attached) | --- |
| 04 | Un-signed draft MTA for PK/PD Studies between Mahidol Oxford Tropical Medicine Research Unit & Aga Khan University Hospital, Karachi. | We have attached the signed MTA between Mahidol Oxford Tropical Medicine Research Unit and Aga Khan University Hospital, Karachi. | --- |
| 05 | It is informed that, there is no GMP certificate attached with a reply dated l6th November 2022.It is again informed that, CoA are not replacement of CoPP as CoPP is mandatory requirement Under Bio-study Rules, 2017.It is therefore again requested to provide CoPP for following products:<br>a) Ensitrelvir fumaric acid 125mg<br>b) Sotrovimab (500mg/8ml) Infusion<br>c) Evusheld Tixagevimab 150mg & Cligavimab 150mg | We have attached the GMP certificate for Ensitrelvir fumaric acid 125 mg again. Since the drug has been authorized for emergency use only so we could not get the CoPP from the manufacturer, so we are providing a Statement of emergency use approval letter from Shionogi. For Sotrovimab and Evusheld, we have removed the drugs from protocol version 0.4<br>(refer to page 7 of Protocol 0.4) | --- |
| 06 | CoPP of other IMPs as mentioned in the protocol, which are not included in the list with dossier need to be provided. | The drugs mentioned in schedules 16.1 to16.7 (Appendix 4 protocol page 37) are part of the site-specific protocol and we have | --- |

| | | | |
|---|---|---|---|
| | | already provided the required documents for those IMPs. | |

19. It is informed that, technical documents (Protocol, IB & Pre-Clinical Studies) were shared through email to all CSC members for technical evaluation & expert opinion, but no comments received.

20. Submitted for consideration, deliberation, discussion & decision of the CSC, please.

**Decision:**

The CSC after detailed discussion and deliberation decided to approve the Phase-II Clinical Trial titled, "Finding Treatments for COVID-19: A Phase-II, Multi-Centre, Adaptive Platform Trial to Assess Antiviral Pharmacodynamics in Early Symptomatic COVID-19 (PLATCOV)", under the Bio-Study Rules, 2017, to be conducted at M/s Aga Khan University Hospital, Karachi. (CTS-0003).

2. A total of 250 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:

i. FAVUZA (Favipiravir 200 mg tablet) Total 3960 Tablets
ii. IZATO (Nitazoxanide 500 mg tablet) Total 2520 tablets
iii. MONUVIR (Molnupravir 200 mg Capsule) Total 2400 capsules
iv. Nirmatrevir/ritonavir (Nirmatrevir: 150 mg tablet; Ritonavir: 100 mg tablet)
    a. Nirmatrevir: Total 1200 tablets
    b. Ritonavir: Total 600 tablets
v. Fluoxetine (20 mg Flux tablet) Total 840 Tablets
vi. Ensitrelvir (Each tablet contains Ensitrelvir fumaric acid 125 mg) Total 420 Tablets
vii. B REGN-COV2 (600 mg Casirivimab/600 mg Imdevimab) Total 60 vials
viii. Sotrovimab (500 mg/8 ml) Total 60 vials
ix. A combination of Molnupiravir and Nirmatrevir/ritonavir
    a. Molnupiravir: Total 2400 tablets
    b. Nirmatrevir: Total 1200
    c. Ritonavir: Total 600 tablets
x. Evusheld (150 mg of the tixagevimab and 150 mg of the Cligavimab) Total 120 vials.

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**AGENDA ITEM XXXIV:**

**APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "A PHASE-III, MULTICENTRE. RANDOMIZED, DOUBLE-BLIND, 24-WEEK STUDY OF THE CLINICAL AND ANTIVIRAL EFFECT OF S-217622 COMPARED WITH PLACEBO IN NON-HOSPITALIZED PAI1ICIPANTS WITH COVID-19", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-25/2023-CT (PS)**

Application was received from Dr. Sayed Faisal Mahmood, CNIC number: 42301-1116154-5, PI of applied trial & Associate Professor & Section Head Infectious Diseases, Department of Medicine, The Aga Khan University Hospital, Karachi, Pakistan, Stadium Road, Karachi dated 12th December, 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. 742806539768, dated 13th December, 2022. The trial is also enlisted on U.S National Trial Registry with identification number ***NCT05305547*** *(https://clinicaltrials.gov/ct2/show/NCT05305547 ).*

02. Applicant informed that, it is a multi-country/multi-center trial & will be conducted in UAE, Argentina, Belgium, Brazil, Columbia, Egypt, Ghana, India, Japan, Kenya, Malawi, Mexico, Pakistan, Peru, Philippines, Poland, South Africa, Tanzania, Thailand, Turkey, Uganda, United States, and

Zimbabwe. Globally approximately 1490 pa11icipants (745 on S-217622 and 745 on placebo) will be randomized into the study. In Pakistan 101 (at present 84 patients are described) Subjects will be recruited on following Clinical Trial Site(s), subject to DRAP approval:

i. The Aga Khan University Hospital, Karachi (12 Subjects)
ii. The Indus Hospital, Karachi (08 Subjects)
iii. Dow University of Health Sciences, Karachi (08 Subjects)
iv. Sindh Infectious Disease Hospital and Research Center Karachi (08 Subjects)
v. Central Park Teaching Hospital, Lahore (08 Subjects)
vi. National Hospital and Medical Centre, Lahore (08 Subjects)
vii. Rehman Medical Institute, Peshawar (08 Subjects)
viii. Shifa International Hospital Islamabad (08 Subjects)
ix. Maroof International Hospital, Islamabad (08 Subjects)
x. Akram Medical Complex Lahore (08 Subjects)

- Subjects with active Covid-19 who meets the inclusion and do not meet the exclusion criteria will be randomized into any of the following two groups.
- -a group treated with S-217622 at a dose of 3 75 mg (3 tablets) for Day 1 and 125 mg (1 tablet) for Days 2 to 5 once daily
- -a group treated with Placebo for S-217622 administered once daily for 5 days (Days 1 to 5 [3 tablets on Day 1 and 1 tablet on Days 2 to 5])

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

i. **Sponsor:** Shionogi, Japan.

ii. **Collaborators**: National Institute of Allergy and Infectious Diseases (NIAID).

iii. **Purpose of trial:** The main aim of this study is to evaluate the efficacy of S-217622 versus placebo among participants who are in the subpopulation of participants who were not expected to receive standard-of-care COVID-19 Group A therapy (defined as monoclonal antibody [mAb] treatment or outpatient intravenous [IV] Remdesivir). Coronaviruses (CoVs) are positive-sense, single-stranded, enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past 2 decades, emerging pathogenic Co Vs capable of causing life-threatening disease in humans and animals have been identified, namely, SARSCoV-1 in 2002 to 2003 and Middle East Respiratory Syndrome corona virus (MERS-Co V) in 2012.

**New Threat**

- A novel pneumonia caused by a previously unknown beta coronavirus emerged in Wuhan, China, in December 2019. The virus is closely related to SARS-CoV-1, which caused an outbreak in 2003, and has been named SARS-Co V-2. The human disease caused by SA RS-Co V-2 is called COVID-19. During the current SARS-Co V-2 outbreak, the incidence of known cases has rapidly increased. On January 30, 2020, the International Health Regulations Emergency Committee of the WHO declared the COVID-19 outbreak a Public Health Emergency of International Concern. On January 31, 2020, the United States (US) Department of Health and Human Services declared a public health emergency in the US. Despite quarantine measures, SARS-CoV-2 has spread widely. As of April 2022, there have been >508 million confirmed cases of COVID-19 and >6 million deaths attributed to COVID-19 globally. Global efforts to evaluate novel antivirals and therapeutic interventions to treat COVID-19 have intensified. Therefore, there is an urgent public health need for rapid development of novel interventions.

**Disease Course**

Once infection occurs, the clinical course is variable. Previous data suggest that fewer than 2.5% of infected persons will show symptoms within 2.2 days (confidence interval [CI], 1.8 to 2.9 days) of exposure, and symptom onset will occur within 11.5 days (Cl, 8.2 to 15.6 days) for 97.5% of infected persons that do develop symptoms. In most ( ~80%) cases, COVID-19 presents as a mild-to-moderately severe, self-limited. acute respiratory illness with fever, cough, and shortness of breath. It remains unclear exactly what the rate of progression of COVID-19 is and what the predictors are for complications, including pneumonia, thromboembolic disease, acute respiratory distress syndrome (ARDS), kidney failure, and death. It is clear that older age, male sex, and comorbidities, including obesity, diabetes, and hypetiension, increase the risk for worse outcomes. In an early meta-analysis, the main clinical symptoms were fever (88.5%), cough (68.6%), myalgia or fatigue (35.8%), expectoration (28.2%), and dyspnea (21.9%). Minor symptoms included headache or dizziness ( 12.1 %), diarrhea ( 4.8%), and nausea and vomiting (3 .9% ). Laboratory
examinations showed that lymphocytopenia (64.5%), increase of C-reactive protein (CRP) (44.3%), leukocytopenia (29.4%), and increase of lactate dehydrogenase (LOH) (28.3%) were more common in those hospitalized with COVID-19.

**iv. Quantity of IMPs required along with justification:**

| IMPs | Molecule | Strength | Pack Size | Manufacturer | No. of Patients | Per Patie | Frequency | TOTAL |
|---|---|---|---|---|---|---|---|---|

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | **nt Does** | | |
| S-217622 (S-217622 fumaric acid: drug substance) | S-217622 is an inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 3C-like (3CL) protease, which is essential for the processing of the polyprotein encoded by a SARS-Cov-2 gene as well as for the replication of the virus | Dosage formulation: 125 mg – Unit Dose Strength | One blister pack of S-217622 or placebo containing 7 tablets will be dispensed to each participant.<br><br>S-217622 tablet: Supplied as a white, 9-mm round tablet. (Store at 15-30°C) | M/s Shionogi Pharma Co., Ltd., 5-1, Mishima 2-chome Settsu, Osaka 566-0022, Japan | 84 (Enrolled + 30%) | 07 tablets | S-217622 at a dose of 375 mg (3 tablets) for Day 1 and 125 mg (1 tablet) for day 2 to 5 once daily. | 7x84 =588 |
| Placebo | Matching placebo | -- | Placebo for S-217622: Supplied as a white, 9-mm round tablet to visually match the active drug. (Store at 15-30°C) | M/s Pharmira Co., Ltd., 2 Chome 1-3, Kuise Terajima, Amagasaki, Hyogo, 660-0813, Japan. | 84 (Enrolled + 30%) | 1 Dose of Saline at Visit 2 | Placebo for S-217622 administered once daily for 5 days (Days 1 to 5 [3 tablets on Day 1 & 1 tablet on day 2-5]) | 7x84 =588 |
| Packaging site: Fisher Clinical Services UK Limited<br>Packaging site address: Langhurstwood Road, Horsham, RH12 4QD, United Kingdom | | | | | | | | |

**a. Source of IMPs:**

- M/s Shionogi Pharma Co., Ltd., 5-1, Mishima 2-chome Settsu, Osaka 566-0022, Japan. (Manufacturer of IMP & Placebo)
- M/s Pharmira Co., Ltd., 2 Chome 1-3, Kuise Terajima, Amagasaki, Hyogo, 660-0813, Japan.
- Fisher Clinical Services UK Limited, Langhurstwood Road, Horsham, RH12 4QD, United Kingdom (Packaging & Shipment services of IMPs to Pakistan)

**b. Wastage and Damage% will be 25%:**

Active: 588 x 30% = 176; Total Import Quantity: 588 + 176 = 764

Placebo: 588 x 30% = 176; Total Import Quantity: 588 + 176 = 764

- Other items to be imported for the trail:
  - Lab Kits (Details & quantity not mentioned)
  - eCoA (Details & quantity not mentioned)

**v. Number of subjects to be recruited:** 1490 Subjects (Globally) 84 Subjects in Pakistan

**vi. Anticipated cost of the project:** USD 200,000/-

**vii. Study design & details:**

| | |
|---|---|
| Study type | Interventional (Clinical Trial) |
| Estimated Enrollment : | 1490 participants (Globally) |
| Allocation: | Randomized |
| Intervention Model: | Parallel Assignment |
| Masking: | Double (Participant & Investigator) |
| Primary Purpose: | Treatment |
| Official Title: | A Phase 3, Multicenter, Randomized, Double-Blind, 24-Week Study of the Clinical and Antiviral Effect of S-217622 Compared With Placebo in Non-Hospitalized Participants With COVID-19 |
| Estimated Study Start Date : | 03 August, 2022 |
| Estimated Primary Completion Date : | 13th October, 2023 |

| | |
|---|---|
| Estimated Study Completion Date : | 13th October, 2023 |

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

| Site(s) |
|---|
| The Aga Khan University Hospital, Karachi |
| The Indus Hospital, Karachi |
| Dow University of Health Sciences, Karachi |
| Sindh Infectious Disease Hospital and Research Center Karachi |
| Central Park Teaching Hospital, Lahore |
| National Hospital and Medical Centre, Lahore |
| Rehman Medical Institute, Peshawar |
| Shifa International Hospital Islamabad |
| Maroof International Hospital, Islamabad |
| Akram Medical Complex Lahore |

Primary Outcome Measures:

i. Median Time to Sustained Symptom Resolution [ Time Frame: Up to Day 29]

Secondary Outcome Measures:

i. Change From Baseline in Quantitative log10 SARS-CoV-2 RNA Levels by Polymerase Chain Reaction (PCR) on Nasopharyngeal (NP) Swab at Day 4 [ Time Frame: Baseline, Day 4]
ii. Percentage of Participants With Adjudicated Hospitalization Due to COVID-19 or Death Due to Any Cause [ Time Frame: Up to Day 29]
iii. Percentage of Participants With Detectable SARS-CoV-2 Viral Culture on NP Swab at Day 4 [ Time Frame: Day 4]
iv. Median Time to Sustained Symptom Resolution Among Subgroups [ Time Frame: Up to Day 29 ]
Subgroups will include high risk versus low risk at enrollment, COVID-19 vaccination status, receipt of COVID-19 treatments, and time from symptom onset at enrollment.

v. Percentage of Participants With Detectable SARS-CoV-2 Viral Culture on NP Swab at Day 4 Among Subgroups [ Time Frame: Day 4 ]
Subgroups will include high risk versus low risk at enrollment, COVID-19 vaccination status, receipt of COVID-19 treatments, and time from symptom onset at enrollment.

vi. Percentage of Participants With Hospitalization (All Cause) or Death Due to Any Cause [ Time Frame: Up to Day 29 ]
vii. Percentage of Participants With Detectable SARS-CoV-2 Viral Culture on NP Swab at Day 8 [ Time Frame: Day 8 ]
viii. Percentage of Participants With NP SARS-CoV-2 RNA Levels by Quantitative PCR Below the Lower Limit of Quantification on Days 4 and 8 [ Time Frame: Days 4 and 8 ]
ix. Median Change From Baseline of SARS-CoV-2 RNA by Quantitative PCR in NP Swabs on Days 4 and 8 [ Time Frame: Baseline, Days 4 and 8 ]
x. Percentage of Participants With Undetectable Viral Culture From Nasopharyngeal Samples on Days 4 and 8 [ Time Frame: Days 4 and 8 ]
xi. Median Time to Self-Reported Return to Usual (Pre-COVID-19) Health [ Time Frame: Up to Day 29 ]
xii. Percentage of Participants at Each Clinical Status as Assessed by a 7-Point Ordinal Scale [ Time Frame: Day 29 ]
xiii. Percentage of Participants With Resting Peripheral Oxygen Saturation ≥96% [ Time Frame: Up to Day 29 ]
xiv. Number of Participants With Adverse Events [ Time Frame: Up to Week 24 ]
xv. Change From Baseline in Short Form 36 Version 2.0 (SF-36 V2) Quality of Life Score [ Time Frame: Baseline, Week 24 ]
xvi. Change From Baseline in EuroQol 5 Dimension 5 Level (EQ-5D-5L) Index Score [ Time Frame: Baseline, Week 24 ]
xvii. Change From Baseline in Post-Acute COVID-19 Questionnaire [ Time Frame: Baseline, Week 24 ]
xviii. Percentage of Participants Who Experienced Death Due to Any Cause [ Time Frame: Up to Week 24 ]
xix. Plasma Concentration of S-217622 [ Time Frame: 60 and 90 minutes post dose on Day 1 and pre-dose on Day 4 ]

05. 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. 742806539768, dated 13th December, 2022. |
| 3 | Investigator Brochure (s) | Attached<br>Edition: # 04, Dated: 30th June, 2022 |
| 4 | Final protocol | Attached<br>SCORPIO-HR, Protocol No. ACTIV-2d/A5407<br>Version 3.0, dated 23rd June, 2022<br><br>* Financing & Insurance details should be part of protocol as per ICH-GCP guidelines. |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached.<br>* Insurance details for subjects need to be included in Inform Consent Form. |
| 6 | List of participating countries | UAE, Argentina, Belgium, Brazil, Columbia, Egypt, Ghana, India, Japan, Kenya, Malawi, Mexico, Peru, Philippines, Poland, South Africa, Tanzania, Thailand, Turkey, Uganda, United States, Zimbabwe 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. | **Wastage and Damage% will be 25%:**<br>Active: 588 x 30% = 176; Total Import Quantity: 588 + 176 = **764 Tablets**<br>Placebo: 588 x 30% = 176; Total Import Quantity: 588 + 176 = **764 Tablets** |
| 9 | Site of the trial | i. The Aga Khan University Hospital, Karachi (CTS-0003)<br>ii. The Indus Hospital, Karachi (CTS-0047)<br>iii. Dow University of Health Sciences, Karachi (It needs to be clarified that which site of DUHS will participate in the trial)<br>iv. Sindh Infectious Disease Hospital and Research Center Karachi<br>v. Central Park Teaching Hospital, Lahore<br>vi. National Hospital and Medical Centre, Lahore<br>vii. Rehman Medical Institute, Peshawar<br>viii. Shifa International Hospital Islamabad<br>ix. Maroof International Hospital, Islamabad<br>x. Akram Medical Complex, Lahore.<br>* Licences of all proposed site(s) along with site PI, need to be provided, so their status & feasibility for the trial may be verified. |
| 10 | Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members. | IRB approval of following CTS are attached:<br>i. IRB/ERC approval of **Aga Khan University Hospital**, **Karachi** dated 25th October, 2022 for a period of one year is attached. (469-471/Corr.)<br>ii. IRB/ERC approval of **Central Park Hospital, Lahore**, dated 12th September, 2022 for a period of one year is attached. (450-453/Corr.)<br>iii. IRB/ERC approval of **Indus Hospital & Health Network, Karachi**, dated 28th November, 2022, for a period of one year is attached. (454-456/Corr.)<br>iv. IRB/ERC approval of **Rehman Medical Institute, Peshawar**, dated 18th November, 2022, for a period of one year is attached. (457-517/Corr.) |

| | | |
|---|---|---|
| | | v. IRB/ERC approval of **National Hospital & Medical Center, Lahore**, dated 11th October, 2022, for a period of one year is attached. (461-464/Corr.)<br>vi. IRB/ERC approval of **Shifa International Hospital Limited, Islamabad**, dated 02nd September, 2022, for a period of one year is attached. (465-468/Corr.)<br>vii. IRB/ERC approval of **Akram Medical Complex, Lahore,** dated 07th October, 2022, is attached. (472-474/Corr.)<br>viii. IRB/ERC approval of **Maroof International Hospital, Islamabad**, dated 14th September, 2022 is attached. (475-525/Corr.)<br>ix. IRB/ERC approval of **DUHS for Dow University of Health Sciences, Karachi & Sindh infectious Diseases Hospital 7 research Center, Karachi**, dated 08th November, 2022 is attached. (478-479/Corr.) (IRB/ERC approval letter is without any information that which documents has been reviewed by the committee, Reference number is also written by hand)<br><br>* IRB Composition along with their notification of following sites(s) are not attached:<br>i. M/s Indus Hospital & Health Network, Karachi.<br>ii. Rehman Medical Institute, Peshawar (Details regarding IRB/ERC members along with designation need to be provided & composition should be as per ICH-GCP Guidelines)<br>iii. Akram Medical Complex, Lahore (Details regarding IRB/ERC members along with designation need to be provided & composition should be as per ICH-GCP Guidelines)<br>iv. Maroof International Hospital, Islamabad. (Details regarding IRB/ERC members along with designation need to be provided & composition should be as per ICH-GCP Guidelines) |
| 11 | Approval of National Bio-ethics Committee (NBC) | Approval reference letter No.4-87/COVID-122/22/672, dated 02th November, 2022 for a period of **Six months** is attached. |
| 12 | CV's of the Investigators | CVs of following (PI & Co-PI) experts are attached.<br>i. Dr. Faisal Mahmood (National-PI) (Page 428-448/Corr.)<br>ii. Dr. Saima Saeed, Site-PI (Page 338-339/Corr.)<br>iii. Dr. Muneeba Ahsan Sayeed, Site-PI (Page 340-343/Corr.)<br>iv. Dr. Azizullah Khan Dhilloo, Site-PI (Page 344-347/Corr.)<br>v. Dr. Ejaz A. Khan Site-PI (Page 352-372/Corr.)<br>vi. Dr. Nadia Majeed, Site-PI (Page 373-374)<br>vii. Dr. Sajjad Naseer, Site-PI (Page 375-388/Corr.)<br>viii. Prof. Dr. Javed Akram Site-PI (Page 389-416/Corr.)<br>ix. Dr. Sajjad, Site-PI (Page 417-427/Corr.)<br>x. Prof. Dr. Javed Akram, Site-PI<br>xi. Dr. Muhammad Ahmad (Page 348-351/Corr.) (Site details not provided) |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | GMP Certificate(s) of following manufacturer(s) are attached:<br>• M/s Shionogi Pharma Co., Ltd., 5-1, Mishima 2-chome Settsu, Osaka 566-0022, Japan. (Manufacturer of IMP & Placebo)<br>• Fisher Clinical Services UK Limited, Langhurstwood Road, Horsham, RH12 |

| | | |
|---|---|---|
| | | 4QD, United Kingdom (Packaging & Shipment services of IMPs to Pakistan)<br><br>GMP Certificate for following is not provided:<br>• M/s Pharmira Co., Ltd., 2 Chome 1-3, Kuise Terajima, Amagasaki, Hyogo, 660-0813, Japan.<br>* CoPP are not applicable as IMP is not registered yet. |
| 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. | Number of patients enrolled at each site in Pakistan:<br>i. The Aga Khan University Hospital, Karachi (12 Subjects)<br>ii. The Indus Hospital, Karachi (08 Subjects)<br>iii. Dow University of Health Sciences, Karachi (08 Subjects)<br>iv. Sindh Infectious Disease Hospital and Research Center Karachi (08 Subjects)<br>v. Central Park Teaching Hospital, Lahore (08 Subjects)<br>vi. National Hospital and Medical Centre, Lahore (08 Subjects)<br>vii. Rehman Medical Institute, Peshawar (08 Subjects)<br>viii. Shifa International Hospital Islamabad (08 Subjects)<br>ix. Maroof International Hospital, Islamabad (08 Subjects)<br>x. Akram Medical Complex Lahore (08 Subjects)<br>Total 84 subjects to be enrolled in Pakistan.<br>Total 1490 Subjects to be enrolled globally. |
| 19 | Name of Monitors & Clinical Research Associate | M/s Iqvia Solutions Pakistan.<br>• Karachi: Bharti Kachela & Sadia Hashmi<br>• Islamabad: Asjid Ali Arshad, Sidra Rashid<br>• Lahore: Mahir Ahmed, Hasina Sarwar & Muhammad Asif Mahmood |
| 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 | 2 years August-2022 (FPI) till 28-Feb-2024 (close out) |
| 23 | Undertaking on Stamp paper | Attached. |

06. 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. $Q^2$ Laboratory):

i. Investigator Instructions Manual
ii. $Q^2$ Laboratory Manual
iii. Material Transfer Agreement

07. Furthermore, applicant also provided following justification(s) provided by the Sponsor:

i. Rationale for vulnerable patient population inclusion (Page 636-637/Corr.)
ii. Justification for the use of placebo (Page 638-629/Corr.)

08. After initial scrutiny following shortcomings are recorded:

i. Details regarding other items need to be imported is not provided for following:
   - Lab Kits (Details & quantity not mentioned)
   - eCoA (Details & quantity not mentioned)
ii. Details regarding trial subject's insurance & compensation is not be included in Inform Consent Form.
iii. Licences of all proposed site(s) along with site PI, need to be provided, so their status & feasibility for the trial may be verified.
iv. IRB Composition along with their IRB/ERC notification of following sites(s) needs to be provided (should be according to ICH-GCP Guidelines & the Bio-Study Rules, 2017):
   - M/s Indus Hospital & Health Network, Karachi.
   - Rehman Medical Institute, Peshawar.
   - Akram Medical Complex, Lahore.
   - Maroof International Hospital, Islamabad.
v. IRB/ERC approval of DUHS for Dow University of Health Sciences, Karachi & Sindh infectious Diseases Hospital 7 research Center, Karachi, dated 08th November, 2022 is attached, but IRB/ERC approval letter is without any information that which documents has been reviewed by the committee, Reference number is also written by hand.
vi. GMP Certificate & role in IMP manufacturing/packaging of following is not provided:
   - M/s Pharmira Co., Ltd., 2 Chome 1-3, Kuise Terajima, Amagasaki, Hyogo, 660-0813, Japan.
vii. Number of subjects to be enrolled in Pakistan is 101 subjects but when calculated as site wise distribution provided it becomes 84, clarification required.

09. Accordingly, after approval shortcomings shared through letter bearing even number dated 03rd February, 2023.

10. Reply received through email on 3rd February, 2023. Summary of submitted reply is as f along with attachments is as follows:

| Sr. No. | Descriptions / Shortcomings | Reply | Remarks |
|---|---|---|---|
| i. | Details regarding other items need to be imported is not provided for following:<br>• Lab Kits (Details & quantity not mentioned)<br>• eCoA (Details & quantity not mentioned) | Please find attached updated document i.e. items to be imported in Pakistan with the eCoA and the lab kits details. (Attachment. 1)<br>All the items will import temporary as per Customs rule and will return back after the procedure. Sponsor will cover all customs related documentation and PTA NOC at the time of import | --- |
| ii. | Details regarding trial subject's insurance & compensation is not be included in Inform Consent Form. | Please refer to ICF on pg. no 19 section 14 &<br>section 16.<br>Insurance certificate is already provided.<br>Please find attached. | --- |
| iii. | Licences of all proposed site(s) along with site PI, need to be provided, so their status & feasibility for the trial may be verified. | Please find attached licenses of the sites. Please note that the following sites have applied for renewal of license;<br>i. AKUH, Karachi. | --- |

| | | | |
|---|---|---|---|
| | | ii. National Hospital & Medical Centre, Lahore<br>iii. Shifa International Hospital, Islamabad<br>iv. Akram Medical Complex<br>v. The individual sites approvals are optional and subject to the DRAP CSC decision. | |
| iv. | IRB Composition along with their IRB/ERC notification of following sites(s) needs to be provided (should be according to ICH-GCP Guidelines & the Bio-Study Rules, 2017):<br>• M/s Indus Hospital & Health Network, Karachi.<br>• Rehman Medical Institute, Peshawar.<br>• Akram Medical Complex, Lahore.<br>• Maroof International Hospital, Islamabad. | Please find attached the respective IRB approvals along with the members list.<br>All the IRB approvals are according to ICH-GCP Guidelines. | --- |
| v. | IRB/ERC approval of DUHS for Dow University of Health Sciences, Karachi & Sindh infectious Diseases Hospital 7 research Center, Karachi, dated 08th November, 2022 is attached, but IRB/ERC approval letter is without any information that which documents has been reviewed by the committee, Reference number is also written by hand. | Please find attached the updated IRB approval for DOW & SIDH enclosing the list the documents approved. | --- |
| vi. | GMP Certificate & role in IMP manufacturing/packaging of following is not provided:<br>• M/s Pharmira Co., Ltd., 2 Chome 1-3, Kuise Terajima, Amagasaki, Hyogo, 660-0813, Japan. | M/s Pharmira is not manufacturing site for Pakistan. The Shinogi Pharma is the main manufacturing site and Fisher is the packaging site for study IP for Pakistan. The GMP Certificates & statement of both is attached. Kindly find the updated IP justification document in attachment. | --- |
| vii. | Number of subjects to be enrolled in Pakistan is 101 subjects but when calculated as site wise distribution provided it becomes 84, clarification required. | The recruitment is competitive and maximum numbers for Pakistan is planed up to 101 so far. However current distribution as per COVID situation is 84 only. In case of availability of subjects, Sponsor can request for 17 more patients. | --- |

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

**Decision:**

The CSC after detailed discussion and deliberation decided to approve the Clinical Trial titled, "A Phase-III, Multicentre, Randomized, Double-Blind, 24-Week Study of the Clinical and Antiviral Effect of S-217622 Compared with Placebo in Non-Hospitalized Participants with COVID-19", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site(s) except Akram Medical Complex, Lahore:

i. The Aga Khan University Hospital, Karachi (12 Subjects)
ii. The Indus Hospital, Karachi (08 Subjects)
iii. Dow University of Health Sciences, Karachi (08 Subjects)
iv. Sindh Infectious Disease Hospital and Research Center Karachi (08 Subjects)
v. Central Park Teaching Hospital, Lahore (08 Subjects)
vi. National Hospital and Medical Centre, Lahore (08 Subjects)
vii. Rehman Medical Institute, Peshawar (08 Subjects)
viii. Shifa International Hospital Islamabad (08 Subjects)
ix. Maroof International Hospital, Islamabad (08 Subjects)

2. A total of 84 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:

| IMPs | Molecule | Strength | Pack Size | Manufacturer | No. of Patients | Per Patient Does | Frequency | TOTAL |
|---|---|---|---|---|---|---|---|---|
| S-217622 (S-217622 fumaric acid: drug substance) | S-217622 is an inhibitor of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 3C-like (3CL) protease, which is essential for the processing of the polyprotein encoded by a SARS-Cov-2 gene as well as for the replication of the virus | Dosage formulation: 125 mg – Unit Dose Strength | One blister pack of S-217622 or placebo containing 7 tablets will be dispensed to each participant.<br><br>S-217622 tablet: Supplied as a white, 9-mm round tablet. (Store at 15-30°C) | M/s Shionogi Pharma Co., Ltd., 5-1, Mishima 2-chome Settsu, Osaka 566-0022, Japan | 84 (Enrolled + 30%) | 07 tablets | S-217622 at a dose of 375 mg (3 tablets) for Day 1 and 125 mg (1 tablet) for day 2 to 5 once daily. | 7x84 =588 |
| Placebo | Matching placebo | -- | Placebo for S-217622: Supplied as a white, 9-mm round tablet to visually match the active drug. (Store at 15-30°C) | M/s Pharmira Co., Ltd., 2 Chome 1-3, Kuise Terajima, Amagasaki, Hyogo, 660-0813, Japan. | 84 (Enrolled + 30%) | 1 Dose of Saline at Visit 2 | Placebo for S-217622 administered once daily for 5 days (Days 1 to 5 [3 tablets on Day 1 & 1 tablet on day 2-5]) | 7x84 =588 |
| Packaging site: Fisher Clinical Services UK Limited<br>Packaging site address: Langhurstwood Road, Horsham, RH12 4QD, United Kingdom | | | | | | | | |

**a. Source of IMPs:**

- M/s Shionogi Pharma Co., Ltd., 5-1, Mishima 2-chome Settsu, Osaka 566-0022, Japan. (Manufacturer of IMP & Placebo)
- M/s Pharmira Co., Ltd., 2 Chome 1-3, Kuise Terajima, Amagasaki, Hyogo, 660-0813, Japan.
- Fisher Clinical Services UK Limited, Langhurstwood Road, Horsham, RH12 4QD, United Kingdom (Packaging & Shipment services of IMPs to Pakistan)

**b. Wastage and Damage% will be 25%:**

Active: 588 x 30% = 176; Total Import Quantity: 588 + 176 = 764

Placebo: 588 x 30% = 176; Total Import Quantity: 588 + 176 = 764

- Other items to be imported for the trial:

- Lab Kits (Details & quantity not mentioned)
- eCoA (Details & quantity not mentioned)

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**AGENDA ITEM XXXV:**

**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 signalling 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<br>Participant in the treatment arm will receive a daily dose of the probiotic Vivomixx for 8 weeks. | Drug: VSL#3<br>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.<br>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.<br>Other Name: Vivomixx |

| | |
|---|---|
| | Device: CapScan®<br>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<br>Participant in the control arm will receive a daily dose of a placebo (microcrystalline cellulose) for 8 weeks. | Device: CapScan®<br>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.<br><br>Drug: Placebo<br>The placebo for the experimental drug VSL#3 (Vivomixx) is microcrystalline cellulose. It is similar in appearance to VSL#3.<br>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.<br>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) |
|---|
| Matiari Research Office, Matiari District, Sindh |

**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<br>Version 1.1, Dated: 14th February, 2022. |
| iv. | Final protocol | Attached<br>Protocol No. MPIGH<br>Version 1.0, dated 06th July, 2022<br><br>* Insurance details not described in trial protocol. |
| v. | Informed consent and participant information sheet (Urdu to English) | Attached. (English & Sindhi)<br>* Urdu version of ICF also need to be developed<br>** 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)<br>* 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:<br>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.<br>i. Dr. Sayed Asad Ali (PI) (Page 316-338/Corr.)<br>ii. Umrani Fayyaz (Page 339-343/Corr.)<br>iii. Najeeha Talat Iqbal (Page 344-373/Corr.)<br>iv. Junaid Iqbal (Page 374-384/Corr.)<br>v. Dr. Sheraz Ahmed (Page 385-389/Corr.)<br>* 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<br>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:<br>Total 76 subjects to be enrolled in Pakistan.<br>Total 76 Subjects to be enrolled globally.<br>* 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. Accordingly, after approval shortcomings shared through letter bearing even number dated 03rd February, 2023, still response is awaited.

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

08.

**Decision:**

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.

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**AGENDA ITEM XXXVI:**

**AMENDMENTS IN INVESTIGATOR'S BROCHURE & INFORMED CONSENT FORM of ALREADY APPROVED CT (CT-0039) TITLED "A PHASE-III, RANDOMIZED, OBSERVER-BLIND, MULTICENTER STUDY TO EVALUATE THE EFFICACY, IMMUNOGENICITY AND SAFETY OF SEQIRUS-CELL-BASED QUADRIVALENT SUBUNIT INFLUENZA VIRUS VACCINE (QIVc) COMPARED TO A NON-INFLUENZA VACCINE WHEN ADMINISTERED IN HEALTHY SUBJECTS AGED 6 MONTHS THROUGH 47 MONTHS", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI.F.No.03-11/2022-CT(PS)**

Application was received from Dr. Fatima Mir, PI of applied trial & Associate Professor, Department of Pediatrics and Child Health, The Aga Khan University Hospital, Karachi, Pakistan, Stadium Road, Karachi dated 09th January, 2023. Wherein request has been made for amendment in Investigator's Brochure & Informed Consent Form of already approved Clinical Trial (CT-0039). Prescribed processing fee of Rs. 25,000/- for Miscellaneous requests paid vide challan number 8262838946, dated 09th January, 2023:

02. Applicant provided following relevant documents:

**i.** Investigator Brochure_Ed3-21-Jul-2022
**ii.** Informed Consent Form [Site 58604-AKU-Main_V5.0PAK(ur)2.0(19 Aug-2022)]
**iii.** Informed Consent Form [Site 58604- AKU-Main_V5.0PAK2.0(19-Aug-2022)]
**iv.** AKUH IRB/ERC approval, dated 23rd December, 2023.

03. Amended Investigator's Brochure & Informed Consent Forms also shared with CSC members through email, for their comments, technical evaluation & expert opinion, but no comments received.

**Decision:**

*The CSC after detailed discussion and deliberation decided to approve the proposed amendments in the following documents:*

***i.*** *Investigator Brochure_Ed3-21-Jul-2022*
***ii.*** *Informed Consent Form [Site 58604-AKU-Main_V5.0PAK(ur)2.0(19 Aug-2022)]*
***iii.*** *Informed Consent Form [Site 58604- AKU-Main_V5.0PAK2.0(19-Aug-2022)]*
**iv.** *AKUH IRB/ERC approval, dated 23rd December, 2023.*

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**AGENDA ITEM XXXVII:**

**APPLICATION FOR APPROVAL OF A PHASE-II CLINICAL TRIAL TITLED, "ACCEPTABILITY AND USABILITY OF A MINIMALLY-INVASIVE CONTINUOUS GLUCOSE MONITORING SYSTEM", FROM BAQAI INSTITUTE OF DIABETOLOGY & ENDOCRINOLOGY, KARACHI. F. No. 03-29/2023-CT (PS).**

Application was received from Prof. Dr. Asher Fawwad, CNIC number: 36302-0366816-9, PI of applied trial & Professor, Baqai Institute of Dialectology & Endocrinology, B‹ Plot No. 1‹ 2 Street 2, Nazimabad Number 2, Karachi, dated 23rd January, 2023, 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. 42289858877, dated 23rd January, 2023.

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

i. **Sponsor:** FIND (Foundation for Innovative New Diagnostics), Geneva, Switzerland.

ii. **Purpose of trial:**

- **The primary objective** of the study is to assess acceptability and usability of a minimally-invasive (MIGM) continuous glucose monitoring system.
- **The secondary objective** of the study is to assess performance of the minimally invasive. CGM in comparison to a blood glucose monitoring system for self-testing.

iii. **Quantity of IMPs/devices imported for trial:**

| S. No. | Product Description | Quantity (Pcs) |
|---|---|---|
| 01 | Sterile applicator | 35 |
| 02 | Detector, charging cradle, charging Cables | 08 |
| 03 | Mock-up applicators | 70 |
| 04 | Mock-up detectors | 08 |
| 05 | iPhones, power supply, charging cables | 10 |

iv. **Source of Investigational Medical Products (IMPs):**

- **Investigational Device:** Fiber Sense CGM System, Eye Sense GmbH, Germany.
- **Other Devices:** Blood glucose monitoring system: Accu-Chek Performa with test strips (CE-marked)

v. **Number of subjects to be recruited:** 30 Subjects

vi. **Anticipated cost of the project:** USD 25,000/-

3. 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. 42289858877, dated 16th January, 2023. |
| iii. | Investigator Brochure (s) | Edition: 1.0, Dated: 31st January, 2022 is attached. |
| iv. | Final protocol | Attached<br>Protocol No. IfDT-2171-FG<br>Version 1.0, dated 13th May, 2022 |

| | | |
|---|---|---|
| v. | Informed consent and participant information sheet (Urdu to English) | Urdu translation is not grammatical & making no sense in sentences.<br>In both (English & Urdu language) consent forms details/information regarding compensation is not included. |
| vi. | List of participating countries | Only 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 | Site approval for generalized Phase-II Clinical Trial is not provided. It is informed BIDE was approved for a specific trial only. |
| x. | Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members. | IRB/ERC composition/notification is not provided. Attached IRB approval is not mentioning that which documents has been reviewed in which meeting of IRB. |
| xi. | Approval of National Bio-ethics Committee (NBC) | Not provided |
| xii. | CV's of the Investigators | CVs of following (PI & Co-PI) experts are attached.<br>**i.** Dr. Asher Fawwad<br>**ii.** Miss Erum Ghafoor<br>**iii.** Rabia Zafar<br>**iv.** Bilal Tahir (irrelevant qualification)<br>**v.** Farrukh Ahmad (irrelevant qualification) |
| xiii. | GMP certificate along with COPP & free sale certificate of the investigational product. | GMP Certificate & CoPP for IMPs 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 enrolled in Pakistan:<br>Up to 30 adult participants with diabetes mellitus type 1 or type 2 |
| 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 | Planned overall duration: from MAY.2022 till DEC.2022 (anticipated).<br>For each individual participant the study duration (active phase) will be: up to 7 days. |
| xxiv. | Undertaking on Stamp paper | Not provided. |

04. After initial scrutiny following shortcomings are recorded:

i. Proposed Clinical trial site is not approved for Phase-II Clinical Trials.
ii. IRB/ERC composition/notification is not provided. Attached IRB approval is not mentioning that which documents has been reviewed in which meeting of IRB.
iii. Approval of National Bio-ethics Committee (NBC) is not provided.
iv. GMP certificate along with COPP & free sale certificate of the investigational product are not provided.
v. Evidence of registration of IMP in the country of origin is not provided.
vi. Planned trial duration (MAY-2022 till DEC-2022) as mentioned in application is already expired.
vii. Undertaking on stamp paper is not provided.
viii. Urdu translation is not grammatical & making no sense in sentences. In both (English & Urdu language) consent forms details/information regarding compensation is not included.
ix. CVs of following experts are attached but their role in trial is not elaborated except of PI
    a. Dr. Asher Fawwad
    b. Miss Erum Ghafoor
    c. Rabia Zafar
    d. Bilal Tahir (irrelevant qualification)
    e. Farrukh Ahmad (irrelevant qualification)

05. Accordingly, after approval shortcomings shared through letter bearing even number dated 03rd February, 2023, still response is awaited.

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

**Decision:**

*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.*
*ii. IRB/ERC composition/notification is not provided. Attached IRB approval is not mentioning that which documents has been reviewed in which meeting of IRB.*
*iii. Approval of National Bio-ethics Committee (NBC) is not provided.*
*iv. GMP certificate along with COPP & free sale certificate of the investigational product are not provided.*
*v. Evidence of registration of IMP in the country of origin is not provided.*
*vi. Planned trial duration (MAY-2022 till DEC-2022) as mentioned in application is already expired.*
*vii. Undertaking on stamp paper is not provided.*
*viii. Urdu translation is not grammatical & making no sense in sentences. In both (English & Urdu language) consent forms details/information regarding compensation is not included.*
*ix. CVs of following experts are attached but their role in trial is not elaborated except of PI*
    *a. Dr. Asher Fawwad*
    *b. Miss Erum Ghafoor*
    *c. Rabia Zafar*
    *d. Bilal Tahir (irrelevant qualification)*
    *e. Farrukh Ahmad (irrelevant qualification)*

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**AGENDA ITEM XXXVIII:**

**APPLICATION FOR AMENDMENT/INCREASE IN SUBJECTS ENROLMENT & INCREASE IN IMP IMPORT IN ALREADY APPROVED CLINICAL TRIAL TITLED "A RANDOMIZED, DOUBLE-MASKED, PARALLEL-GROUP, MULTICENTER CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AVT06 COMPARED WITH EU-EYLEA ® IN SUBJECTS WITH NEOVASCULAR (WET) AGE-RELATED MACULAR DEGENERATION (ALVOEYE)", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-12/2022-CT**

Application from Dr. M.A. Rehman Siddiqui, The Aga Khan University Hospital, Karachi, Pakistan, Stadium Road, Karachi, received on 16th November, 2022. Wherein reply is in reference to this Division's letter even number dated 08th November, 2022.

02. It is submitted that, previously for 28 study Subjects following quantity of IMPs was approved:

| IMP | No. Of Subjects | Per patient Dose | Frequency | Total |
|---|---|---|---|---|
| AVT06 | 14 | 2 mg (0.05 mL) | Subjects will receive 2 mg (0.05 mL) intravitreal injection of AVT06 or Eylea every 4 weeks for 3 consecutive monthly visits (Day 1-, Week 4, and Week 8) followed by every 8 weeks throughout the remaining treatment period (at Weeks 16, 24,32,40, and 48). | 8*14= 112 |
| Eylea | 14 | 2 mg (0.05 mL) | Subjects will receive 2 mg (0.05 mL) intravitreal injection of AVT06 or Eylea every 4 weeks for 3 consecutive monthly visits (Day 1, Week 4, and Week 8) followed by every 8 weeks throughout the remaining treatment period (at Weeks 16, 24,32,40, and 48). | 8*14= 112 |

**Wastage and Damage % will be 25%:**
Active: 112 x 25% = 28; Total Import Quantity: 112 + 28 = 140
Comparator: 112 x 25% = 28; Total Import Quantity: 112 + 28 = 140

03. Applicant now requested for an increase in number of recruitment in Pakistan. P.I. request is as follows:

*Subject: Application for Extended Recruitment Timelines for already approved Clinical Trial (CT-0043)*

*With reference to DRAP reference no. F.No.03-12/2022-CT (PS) and approval no. CT-0043 the Phase-III study, protocol AVT06-GL-C01 titled:* ***"A Randomized, Double-Masked, Parallel-Group, Multicenter Clinical Study to Evaluate the Efficacy and Safety of Avt06 Compared with EU-Eylea ® In Subjects with Neovascular (Wet) Age-Related Macular Degeneration (ALVOEYE)"****. It is to notify you that global recruitment is low and the recruitment period will be extended. Pakistan sites started late, and we would like to give an opportunity and more time to enroll more subjects. As the recruitment is competitive, we are planning more subjects to enroll in.*

*The inclusion of Pakistan will bring an important geographical diversity to the study's dataset and will be key in supporting the endpoints of this trial.*

04. Applicant provided following attachments:

i. Fee challan of prescribed processing fee Rs. 25000/-, paid vide challan no. 496058625228, dated 16th January, 2023. (Page 1379/Corr.)
ii. Letter from Sponsor for extended recruitment (Page 1382/Corr.)
iii. Trial Registration Certificate (Page 1388-1393/Corr.)
iv. Drugs Import Licence (Page 1394-1395/Corr.)
v. Trial Insurance Certificate (Page 1396-1398/Corr.)
vi. Justification for Quantity of Investigational Products to be imported for Clinical Trial in Pakistan

a. **Protocol No.:** AVT06-GL-C01

b. **Protocol Title:** A Randomized, Double-masked, Parallel-group, Multicenter Clinical Study to Evaluate the Efficacy and Safety of AVT06 compared with EU-Eylea® in subjects with Neovascular (wet) Age-related Macular Degeneration (ALVOEYE)."

c. Proposed number of subjects to be enrolled in Pakistan: **42** at 6 No of Sites.

d. **IMP Calculation**: Treatment Plan for extended enrolment of 42 Subjects:

| IMP | No. Of Subjects | Per patient Dose | Frequency | Total |
|---|---|---|---|---|
| AVT06 | 21 | 2 mg (0.05 mL) | Subjects will receive 2 mg (0.05 mL) intravitreal injection of AVT06 or Eylea every 4 weeks for 3 consecutive monthly visits (Day 1-, Week 4, and Week 8) followed by every 8 weeks throughout the remaining treatment period (at Weeks 16, 24,32,40, and 48). | 8*21= 168 |
| Eylea | 21 | 2 mg (0.05 mL) | Subjects will receive 2 mg (0.05 mL) intravitreal injection of AVT06 or Eylea every 4 weeks for 3 consecutive monthly visits (Day 1, Week 4, and Week 8) followed by every 8 weeks throughout the remaining treatment period (at Weeks 16, 24,32,40, and 48). | 8*21= 168 |

***e. Wastage and Damage % will be 30%:***

*Active: 112 x 30% = 50; Total Import Quantity: 168 + 50 = 218*
*Comparator: 112 x 30% = 50; Total Import Quantity: 168 + 50 = 218*

*f. Manufacturer's name and address as per COA and GMP:*

***AVT06:***
*Patheon Italia S.p.A. (part of Thermo Fisher Scientific)*
*Viale G.B. Stucchi 110,*
*20900 Monza (MB), Italy.*

***Eylea:***
*Bayer AG*
*Müllerstraße 178*
*13353 Berlin, Germany.*

***Batch and Expiry:***
*Active: Batch # E230597-0014L Expiry Dec2023*
*Comparator/Placebo: Batch # E230597-0014L Expiry Dec 2023.*

***Packaging site and address:***
*Almac Clinical Services (ACS)*
*20 Seagoe Industrial Estate*
*Craigavon T863 5QD*
*Northern Ireland.*

## Decision:

*The CSC after detailed discussion and deliberation decided to approve the increase in subject enrolment from 28- 42 and import required IMPs* after getting necessary approval/NOC from concerned DRAP field office. *Summary of required quantities of IMPs is as follows:*

a. ***Protocol No.:*** *AVT06-GL-C01*
b. ***Protocol Title:*** *A Randomized, Double-masked, Parallel-group, Multicenter Clinical Study to Evaluate the Efficacy and Safety of AVT06 compared with EU-Eylea® in subjects with Neovascular (wet) Age-related Macular Degeneration (ALVOEYE)."*
c. ***Proposed number of subjects*** *to be enrolled in Pakistan:* ***42*** *at 6 No of Sites.*
d. ***IMP Calculation****: Treatment Plan for extended enrolment of 42 Subjects:*

| *IMP* | *No. Of Subjects* | *Per patient Dose* | *Frequency* | *Total* |
|---|---|---|---|---|
| *AVT06* | *21* | *2 mg (0.05 mL)* | *Subjects will receive 2 mg (0.05 mL) intravitreal injection of AVT06 or Eylea every 4 weeks for 3 consecutive monthly visits (Day 1-, Week 4, and Week* | *8*21= 168* |

| | | | | |
|---|---|---|---|---|
| | | | *8) followed by every 8 weeks throughout the remaining treatment period (at Weeks 16, 24,32,40, and 48).* | |
| *Eylea* | *21* | *2 mg (0.05 mL)* | *Subjects will receive 2 mg (0.05 mL) intravitreal injection of AVT06 or Eylea every 4 weeks for 3 consecutive monthly visits (Day 1, Week 4, and Week 8) followed by every 8 weeks throughout the remaining treatment period (at Weeks 16, 24,32,40, and 48).* | *8*21= 168* |

***e. Wastage and Damage % will be 30%:***
*Active: 112 x 30% = 50; Total Import Quantity: 168 + 50 = 218*
*Comparator: 112 x 30% = 50; Total Import Quantity: 168 + 50 = 218*

*f. Manufacturer's name and address as per COA and GMP:*

***AVT06:***
*Patheon Italia S.p.A. (part of Thermo Fisher Scientific)*
*Viale G.B. Stucchi 110,*
*20900 Monza (MB), Italy.*

***Eylea:***
*Bayer AG*
*Müllerstraße 178*
*13353 Berlin, Germany.*

***Batch and Expiry:***
*Active: Batch # E230597-0014L Expiry Dec2023*
*Comparator/Placebo: Batch # E230597-0014L Expiry Dec 2023.*

***Packaging site and address:***
*Almac Clinical Services (ACS)*
*20 Seagoe Industrial Estate*
*Craigavon T863 5QD*
*Northern Ireland.*

## AGENDA ITEM XXIX:

**APPLICATION FOR AMENDMENT IN PROTOCOL & INFORMED CONSENT FORM OF CLINICAL TRIAL TITLED "RANDOMIZED CONTROLLED TRIAL TO ASSESS THE IMMUNOGENICITY AND SAFETY OF FULL VERSUS FRACTIONAL DOSE OF PFIZER/BIONTECH, ASTRAZENECA, AND SINOVAC COVID-19 VACCINES GIVEN AS A BOOSTER DOSE AT LEAST 6 MONTHS AFTER PRIMARY VACCINATION SERIES OR PCR-CONFIRMED INFECTION WITH SARS-COV-2 IN HEALTHY ADULTS", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-08/2022-CT(PS)**

Application received from Dr. Farah Naz Qamar, Associate Professor, Department of Pediatrics, Aga Khan University Hospital, Stadium Road, Karachi, dated 05th December, 2022. Wherein request has been made for amendment in Protocol & Informed Consent Form of already approved Clinical Trial (CT-0040). Prescribed processing fee of Rs. 25,000/- for Miscellaneous requests paid vide Challan number 79543707 dated 02nd December, 2022.

02. Application is reproduced as under:

*Dear Chairman/Secretary,*

*This letter is to inform you of an amendment in our DRAP approved trial titled "Randomized controlled trial to assess the immunogenicity and safety of full versus fractional dose of Pfizer/BioNTech, AstraZeneca, and Sinovac*

*COVID-19 vaccines given as a booster dose at least 6 months after primary vaccination series or PCR-confirmed infection with SARS-CoV-2 in healthy adults."*

*This trial was testing the immune response for three COVID-19 vaccines namely Pfizer/BioNTech, AstraZeneca and Sinovac given as a booster dose in Brazil and Pakistan. However, due to the no n-availability of the AstraZeneca vaccine in Pakistan the AstraZeneca booster arms of the trial are being dropped on the recommendations of the sponsor. Changes in the study arms do not pose any increased risk to the participants. Initial sample size was calculated for each arm individually and will not affect the power of any particular arm.*

*Attached is the AKUH-ERC and NBC approval letter with the amended protocol for your review and approval. Your kind support for approval of the amendment is appreciated.*

03. Applicant submitted following documents:

- **i.** Amended Protocol (Change Control Copy)
- **ii.** Final Protocol (Sabin CoV 22) Version 2.0, dated 15th November, 2022
- **iii.** Informed Consent Form Version-4
- **iv.** AKUH IRB/ERC approval, dated 29th November,2022 (
- **v.** NBC approval Ref: No.4-87/COVID-106/22/741, dated 06th December,2022.
- **vi.** Fee Deposit Challan-Number: 79543707,

04. Summary of changes is as follows:

***Summary of Changes in Inform Consent Form***

***Protocol Number:*** *Sabin CoV 22*
***Protocol Title:*** *Randomized controlled trial to assess the immunogenicity and safety of full versus fractional dose of Pfizer/BioNTech, AstraZeneca, and Sinovac COVID-19 vaccines given as a booster dose at least 6 months after primary vaccination series or PCR-confirmed infection with SARS-CoV-2 in healthy adults*

| | ***Version Number*** | ***Version date*** |
|---|---|---|
| ***Current approved ICF*** | *Version 3* | *April 13, 2022* |
| ***Amended ICF*** | *Version 4* | *November 15, 2022* |

- *In Page 2 Section study procedures under the AstraZeneca Priming group, AstraZeneca arms have been removed reducing the sub arms from 5 to 3.*
- *In Page 2 Section study procedures under the Natural Infection Priming group, all the 4 sub-arms ((1) Pfizer full dose vaccine as a booster; 2) Pfizer half dose vaccine as a booster; or 3) Pfizer one-third dose vaccine as a booster; or 4) Sinovac full dose as a booster) have been mentioned.*
- *In Page 3, Section: Discomforts, Risks and benefits. The statement that mentions (3) Three vaccines have been reduced to (2) two, removing the AstraZeneca vaccine.*

***Summary of Protocol Changes***

***Protocol Number:*** *Sabin CoV 22*

***Protocol Title:*** *Randomized controlled trial to assess the immunogenicity and safety of full versus fractional dose of Pfizer/BioNTech, AstraZeneca, and Sinovac COVID-19 vaccines given as a booster dose at least 6 months after primary vaccination series or PCR-confirmed infection with SARS-CoV-2 in healthy adults*

| | ***Version Number*** | ***Version date*** |
|---|---|---|
| ***Current approved protocol*** | *Version 1* | *April 12, 2022* |
| ***Amended Protocol*** | *Version 2* | *November 15, 2022* |

- *Page 11, Section "Hypothesis", Point 2 "Brazil only: The immune response from a fractional booster dose of AZD1222 is non-inferior to a full booster dose in adult populations primed through complete vaccination with Sinovac, AZD1222 or BNT162b2." Has been added as AstraZeneca arm has been removed from Pakistan Site.*
- *Page 12, & Page 37, Section: Immunogenicity Objective, comparator arms with AstraZeneca have been removed.*
- *Page 13, & Page 37 Section: Secondary Immunogenicity Objective, comparator arms with AstraZeneca have been specified for Brazil only.*
- *Page 15, Section: Study Design, comparator arms with* ***AstraZeneca have been specified for Brazil only and for Pakistan Subgroups with AstraZeneca has been removed****.*
- *Page 38 Section: Exploratory objectives, comparator arms with AstraZeneca have been specified for Brazil only.*
- *In page 39 Section: Study Design, the study arms have been changed from 16 to 10 for Pakistan and total number of participants have been changed from 1440 to 900.*
- *In Page 42 Section "Treatment arms", arms with AstraZeneca have been specified for Brazil only.*
- *In Page 49-50 Section Randomization scheme, the following paragraph has been added" In Pakistan, participants primed with AZD1222 or BNT162b2 will be randomized to one of 3 booster treatment arms (fractional and full doses of BNT162b2). Participants primed with Sinovac will be randomized to one of 4 booster treatment arms (the additional treatment arm being a full dose Sinovac booster)."*
- *Page 56 Section: Daily diary has been removed as this will not be used in Brazil or Pakistan.*
- *Page 61 section: Pseudo virus neutralization the following section has been added "Samples from Pakistan will be shipped to the CEPI central laboratory for pseudo virus neutralization assays. https://www.surveymonkey.com/r/8K2YWLC"*
- *Page 76, section 13.5, Insurance Policy added in the protocol*.

05. It is informed that, amended protocol version 2.0 (with change control copy), Informed Consent Forms verion-4 & summary of changes, were shared through email to all CSC members for expert opinion, but no comments received.

**Decision:**

*The CSC after detailed discussion and deliberation decided to approve the proposed amendments in the following documents:*

***i.*** *Informed Consent Form Version 4.0, dated 15th November, 2022*
***ii.*** *Protocol Version 2.0, dated 15th November, 2022.*

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