MINUTES OF THE 36TH MEETING OF CSC HELD ON 21ST NOVEMBER, 2022.

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36th Meeting of CSC was held on 21st November, 2022 under the Chairmanship of the Director Pharmacy Services Division in the Committee Room, 4th Floor, Drug Regulatory Authority of Pakistan, Islamabad.

2. The meeting was attended by the following members: -

Sr. No.	Name	Designation
01	**Dr. Noor Muhammad Shah**	Chairman CSC / Director Pharmacy Services.
02	**Dr. Mirza Tasawer Baig.**	Associate Professor in the Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi & Clinical Pharmacist at Dr. Ziauddin Hospital, Karachi. **(Sindh)**
03	**Prof. Munawar Alam Ansari.**	Professor of Pharmacology, Dean Faculty of Pharmacy, Liaquat University of Medical Sciences, Jamshoro. **(Sindh)**
04	**Prof. Dr. Fazal Subhan.**	Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar, **(Khyber Pakhtunkhwa)**.
05	**Dr. Faiza Bashir**	Nominee of Chairman, Pakistan Health Research Council, Islamabad.
06	**Muhammad Adnan Faisal Saim**	Additional Director, Pharmacy Services Division.
07	**Malik Muhammad Asad**	Deputy Director-I, Pharmacy Services Division/ Secretary CSC.
08	**Ahsan Ul Haq Athar**	Deputy Director-II, Pharmacy Services Division-DRAP.
09	**Shafqat Hussain Danish**	Assistant Director, Pharmacy Services Division-DRAP.

3. Following members attended the meeting online through Zoom:

01	**Prof. Dr. Saeed Ahmad Khan**	Professor of Medicine Bolan Medical College Quetta presently serving as head of medicine department Jhalawan medical college Khuzdar. **(Balochistan)**
02	**Mr. Waqas Latif**	Data Analyst/Biostatistician in Quality Enhancement Cell (QEC) at University of Health Sciences, Lahore. **(Punjab)**

4. Chairman, CSC welcomed all the members. Chairman, CSC also thanked members for their active participation. The Deputy Director, Pharmacy Services, presented the agenda as follows:

AGENDA ITEM I:

CONFIRMATION OF THE MINUTES OF THE 35TH CLINICAL STUDIES COMMITTEE'S MEETING.

The minutes of the 35th CSC's meeting were shared with all CSC members through email on 14th October, 2022. 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 were placed again for confirmation/signatures of the members for confirmation.

Decision:

The members confirmed the minutes of 35th meeting of CSC which was held on 13th October, 2022.

AGENDA ITEM II:

SUBMISSION OF CERTIFICATE OF NON CONFLICT OF INTEREST ON AFFIDAVIT BY THE CSC MEMBERS.

Drug Regulatory Authority of Pakistan (DRAP) is endeavouring to adopt international best practices. In this context DRAP is currently working to attain maturity level III in WHO NRA Global Benchmarking Tool, which is considered as baseline for stringent regulatory authorities. DRAP has successfully submitted revised WHO Global Benchmarking Self-Assessment Tool.

2. One of the requirements in the subject matter is the non-conflict of interest, so, that, the acts & decisions of the Committee are not influenced. Accordingly, the document was shared with the honourable members of the Committee.

3. The members were requested to sign the said affidavit regarding non-conflict of interest.

4. Following members provided undertaking on affidavit:

i. *Fazal Subhan, Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar,* ***(Khyber Pakhtunkhwa)***.
ii. *Prof. Dr. Saeed Ahmad Khan*
iii. *Dr. Mirza Tasawer Baig, Associate Professor in the Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi & Clinical Pharmacist at Dr. Ziauddin Hospital, Karachi.* ***(Sindh)***
iv. *Waqas Latif, Data Analyst/Biostatistician in Quality Enhancement Cell (QEC) at University of Health Sciences, Lahore.* ***(Punjab)***

It was requested to other members of the Committee to sign the affidavit and produce it during the next meeting of the Committee.

AGENDA ITEM III:

NOMINATIONS OF CO-OPTED MEMBERS IN CLINICAL STUDIES COMMITTEE, DECISION BY THE AUTHORITY.

Under the Rule 13(1)(j) of the Bio-Study Rules, 2017. CSC has the power to nominate any person as a co-opted member for therapeutic goods or any other specific matter. Accordingly, it was suggested that, the CSC may discuss the matter & may co-opt some members to strengthen the Committee, the Committee may utilize expertise of co-opted members in evaluation of Clinical Research dossiers & may utilize them in pre/post inspection of Clinical Trial Sites, CROs, Bio-analytical Laboratories & BA/BE Studies Centers.

Decision:

The Committee decided that, CVs of experts in the matter will be placed before the Committee for nomination as co-opted members.

AGENDA ITEM IV:

APPROVAL OF CLINICAL TRIAL SITES WITH CLINICAL TRIAL / RATTIFICATION IN THE REQUEST FOR APPROVAL & REGISTRATION OF PHASE-IV CLINICAL TRIAL TITLED "A MULTICOUNTRY, MULTI-CENTER, THREE-ARM, PARALLEL GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIAL OF TWO DOSES OF ANTENATAL CORTICOSTEROIDS FOR WOMEN WITH A HIGH PROBABILITY OF BIRTH IN THE LATE PRETERM PERIOD IN HOSPITAL IN LOW-RESOURCE COUNTRIES TO IMPROVE NEW-BORN OUTCOMES". F. No.03-84/2021-DD (PS)

It is submitted that the subject trial application 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 approve the Clinical Trial titled, "A Multi-country, Multi-Center, Three-Arm, Parallel Group, Double-Blind, Placebo-Controlled, Randomized Trial of Two Doses of Antenatal Corticosteroids for Women with a High Probability of Birth in the Late Preterm Period in Hospital in Low-Resource Countries to Improve New-Born Outcomes", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Sites:

i. *M/s Aga Khan Maternal & Child Care Center (AKMCCC), situated at PLOT #4/2, Main Jamshoro Rd, Hyderabad-Sindh*
ii. *M/s Aga Khan Hospital for Women & Children, Kharadar, situated at Atmaram Pritamdas Rd, Lyari, Karachi, Sindh.*

02. It was told to the Committee informed that, the trial applied was to be carried out at following four (04) Clinical Trial Site(s) but mistakenly only two sites were mentioned in the 35th CSC decision:

i. Clinical Trial Unit, Aga Khan University Hospital Main Campus, Stadium Road, Karachi. (Already approved & licensed under CTS-0003)
ii. Aga Khan Hospital for Women, Garden, Karachi (Already approved & licensed under CTS-0062)
iii. The Aga Khan maternal & Child Care Center (AKMCCC), Hyderabad (Approved in the 35th CSC meeting & granted licence No. CTS-0083)
iv. The Aga Khan Hospital for Women & Children, Kharadar, Karachi (Approved in the 35th CSC meeting & granted licence No. CTS-0084)

03. Registration letter No. CT-0041 was issued on 21st October, 2022 with above mentioned four (04) Clinical Trial Sites. Post-facto approval/ratification from the CSC was therefore requested from the Committee.

Decision:

The CSC accordingly ratified the matter regarding number of Clinical Trial Sites(s) for the subject study & approved the following sites:

i. *Clinical Trial Unit, Aga Khan University Hospital Main Campus, Stadium Road, Karachi. (Already approved & licensed under CTS-0003)*
ii. *Aga Khan Hospital for Women, Garden, Karachi (Already approved & licensed under CTS-0062)*
iii. *The Aga Khan maternal & Child Care Center (AKMCCC), Hyderabad (Approved in the 35th CSC meeting & granted licence No. CTS-0083)*
iv. *The Aga Khan Hospital for Women & Children, Kharadar, Karachi (Approved in the 35th CSC meeting & granted licence No. CTS-0084)*

AGENDA ITEM V:

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. Secretary CSC presented the case before CSC & 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.

AGENDA ITEM VI:

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. * Financing & insurance details are not provided
5	Informed consent and participant information sheet (Urdu to English)	Attached but following points need to be clarified * 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. * 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,	The approximate required quantity of following IMPs will be as follows: i. Aspirin 300mg (Solprin®) Tablets (235 Packs 92s) ii. Esomeprazole/Placebo 40mg Tablets (35 Tablets/bottle) (410 Bottles)

	1976 and application for import of trial material.	
9	Site of the trial	i. Aga Khan University Hospital, Karachi. ii. Aga Khan Hospital for Women & Children, Kharadar, Karachi. * 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. **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). **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. **i.** Dr. Sidrah Nausheen (PI) (117-139/Corr.) **ii.** Dr. Sajid Sufi (Co-PI) (140-179/Corr.) **iii.** Dr. Shabina Ariff (Co-PI) (180-210/Corr.) **iv.** 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: i. Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia. ii. Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India iii. Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia * GMP certificate of all manufacturer issued by respective country drugs regulatory body need to be provided. ** 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. 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. Secretary CSC presented the case before CSC & 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.

AGENDA ITEM VII:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "EFFECTIVENESS OF NOVEL APPROACHES TO RADICAL CURE WITH TAFENOQUINE AND PRIMAQUINE (EFFORT)- A RANDOMIZED CONTROLLED TRIAL IN P. VIVAX PATIENTS". FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-10/2022-DD (PS)

Applicant is from Dr. M. Asim (42201-0543067-7), Professor and Consultant Parasitologist, institutional Lead for APMEN, Former Chair Hospital Ethics Committee, Department of Pathology & Microbiology, Aga Khan University, Stadium Road, Karachi, dated 28th July, 2022. Wherein request has been made for approval of subject Clinical Trial on prescribed Form-II of the Bio-Study Rules, 2017, along with a fee of Rs.200000/- deposited vide challan number: 30174303601,

dated 15th July 2022. The trial is also enlisted on U.S National Trial Registry with identification number NCT04411836 *(https://clinicaltrials.gov/ct2/show/NCT04411836)* (Page 413-418/Corr.)

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

i. **Sponsor:** Menzies School of Health Research, Australia

ii. **Collaborators**:

a. Aga Khan University Hospital, Karachi, Pakistan.
b. University of Melbourne, Australia.
c. National Centre for Parasitology, Entomology and Malaria Control, Cambodia.
d. Mahidol Oxford Tropical Medicine Research Unit, UK.
e. Ethiopian Public Health Institute, Ethiopia.
f. Universitas Sumatera Utara, Indonesia.
g. Arba Minch University, Ethiopia.

iii. **Contact information:** Kamala Thriemer, MD, MPH, PhD
0889468644
kamala.ley-thriemer@menzies.edu.au

iv. **Purpose of trial:** There have been three major advances in the tools available to tackle P. Vivax relapses recently: single dose Tafenoquine (TQ), short course high dose Primaquine (PQ) and a novel quantitative point of care G6PD test. Whilst single dose radical cure with TQ represents a major advance, there are concerns that the pivotal Phase 3 clinical trials were designed for non-inferiority to the low dose PQ regimen. There is increased evidence that in many locations, low dose PQ is inferior to a high dose PQ regimen. Now that the G6PD diagnosis can be assured and short-course high-dose PQ can be administered safely, there is a dire need to compare the safety and efficacy of these alternative treatment strategies. We propose a multicenter open label randomized controlled study to compare the effectiveness of these three key radical cure options, their safety, cost effectiveness and feasibility.

The study is designed as a prospective parallel group randomised controlled superiority effectiveness trial of patients with uncomplicated P. Vivax malaria. For the purpose of study preparation, only patients with a G6PD activity > 70oA of the adjusted male median (AMM) as determined by the Biosensor™ (SD Bioline, ROK) will be eligible for enrolment into the trial. In order to determine l0O% G6PD activity in each site, a total of 30 non-related adult males attending the health facility will be sampled, who will only be included in the pre-study to calculate the local AMM if they are negative for malaria as confirmed by microscopy, no history of fever in the receding 48 hours, no history of malaria, major injury, surgery or blood transfusion within the last 6 months. Written informed consent will be requested along with a 10µl fingerpick sample and G6PD activity will be measured in duplicate using the Biosensor. No follow up of those patients will be required.

Eligible patients who have provided written informed consent will be enrolled into the following treatment arms in a ratio of 1 :1 :1.

a) ***The control arm:*** patients are treated with schizontocidal treatment plus low dose PQ (total dose 3.5mg/kg) unsupervised over 14 days (PQ14)
b) ***The first intervention arm:*** patients are treated with schizontocidal treatment plus high dose PQ (total dose 7 mg/kg) unsupervised over 7 days (PQ7)
c) ***The second intervention arm:*** patients are treated with schizontocidal treatment plus a single dose of Tafenoquine (TQ)

v. Detailed Description:

- To assess the effectiveness of a short-course of high dose Primaquine (total dose 7mg/kg given unsupervised over 7 days) compared to the current standard low dose Primaquine regimen (total dose 3.5mg/kg given unsupervised over 14 days).
- To assess the effectiveness of Tafenoquine (single dose of 300mg) compared to the short-course high dose Primaquine regimen.
- To assess the safety of Tafenoquine compared to the high and low dose Primaquine regimens.
- To assess the cost-effectiveness and feasibility of high dose Primaquine and Tafenoquine compared to the current low dose Primaquine regimen

vi. Study design & details:

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	960 participants (Globally) as per US Trial Registry 720 participants (Globally) as per application & 240 participants in Pakistan.

Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open label)
Primary Purpose:	Treatment
Official Title:	Effectiveness of Novel Approaches to Radical Cure with Tafenoquine and Primaquine - a Randomized Controlled Trial in P. Vivax Patients
Estimated Study Start Date :	25 April, 2021
Estimated Primary Completion Date :	01st June, 2022
Estimated Study Completion Date :	31st December, 2022

vii. Eligibility Criteria:

a. Inclusion Criteria

- P. Vivax peripheral parasitemia (mono-infection) as determined by microscopy.
- G6PD normal status (G6PD activity ≥ 70% of the adjusted male median as determined by the Biosensor™ (SD Biosensor, ROK))
- Fever (temperature ≥37.5ºC) or history of fever in the preceding 48 hours
- Age ≥18 years
- Written informed consent
- Living in the study area and willing to be followed for six months

b. Exclusion Criteria:

- Danger signs or symptoms of severe malaria.
- Anaemia (defined as Hb <8g/dl)
- Pregnant or lactating females
- Known hypersensitivity to any of the study drugs
- Regular use of drugs with haemolytic potential

3. Details regarding Clinical Trial Sites, PI & Co-PI in Pakistan is as follows:

A. Khidmat-e-Alam Medicine centre, Karachi, Nazimabad, Pakistan (Not approved yet)
   - **i.** Principal Investigator: Asim Beg, MD.
   - **ii.** Sub-Investigator: Dr. Najia Ghanchi, MD.
   - **iii.** Sub-Investigator: Dr. Momin Kazi, MD.
   - **iv.** Sub-Investigator: Dr. Farah Qamar, MD.

B. Thatta Civil Hospital, Thatta, Sindh, Pakistan (Not approved yet)
   - **i.** Principal Investigator: Asim Beg, MD.
   - **ii.** Sub-Investigator: Najia Ghanchi, MD.
   - **iii.** Sub-Investigator: Momin Kazi, MD.

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.200000/- deposited vide challan number: 30174303601, dated 15th July 2022.
3	Investigator Brochure (s)	Attached **i.** Kodatef ® (Tafenoquine Succinate) 100mg Tablet (14-27/Corr.) **ii.** Primaquine 15mg Tablets (28-33/Corr.)
4	Final protocol	Attached Version 2.2, dated August, 2022 * In study objective Pakistan is not mentioned. ** Details of trial subject insurance & finance amount is not mentioned.

5	Informed consent and participant information sheet (Urdu to English)	ICF in English, Urdu & Sindhi are attached but following point need to be clarified * It is mentioned in the Informed Consent Form that, "*The study cannot compensate you or pay for life-long or long-term care for study related injuries or for any long-term ill effects to your health*".
6	List of participating countries	Ethiopia, Indonesia, Cambodia & 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.	The approximate required quantity of IMPs are as follows: **i.** Kodatef (Tafenoquine) 100 mg Tablets 19 boxes (16 tablets per box) **Total 304 Tablets** **ii.** Primaquine 15mg Tablets 31 boxes/bottles (250 tablets per box/bottle) **Total 7750 Tablets.** * Justification for IMPs as per number of subject & dosing need to be provided.
9	Site of the trial	a. Khidmat-e-Alam Medical center, Nazimabad, Pakistan. b. Thatta Civil Hospital, Thatta, Sindh province, Pakistan.
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 is 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).
12	CV's of the Investigators	CVs of following are attached. **v.** Dr. Muhammad Asim Beg, AKUH, Karachi (National-PI) (81-110/Corr.) **vi.** Dr. Farah Naz Qamar, AKUH, Karachi (Co-PI) (11-123/Corr.) **vii.** Dr. Abdul Momin Kazi, AKUH, Karachi (Co-PI) (124-149/Corr.) **viii.** Dr. Najia Ghanchi, MD., AKUH, Karachi (Co-PI) (150-164/Corr.) ***** All above PI/Co-PI are from AKUH, Karachi, none of PI/Co-PIs are nominated from proposed CTS(s).
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following IMPs manufacturer(s) are attached: iv. M/s The Government Pharmaceutical Organization, Thailand. v. M/s Piramal Pharma Limited, India. CoPP/Free Sale Certificate(s) of following IMPs are attached: i. Primaquine 15mg Tablets manufactured by M/s The Government Pharmaceutical Organization, Thailand. * CoPP/Free Sale Certificate for Kodatef (Tafenoquine as succinate) 100mg Tablets manufactured by M/s Piramal Pharma Limited, India, or GMP Certificate of M/s Biocelect Pty Ltd., Australia need to be provided & it should be clarified that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the applied Clinical Trial.
14	Pre-clinical/clinical safety studies	Not applicable as both IMPs are registered & PIL are provided: **i.** Kodatef ® (Tafenoquine Succinate) 100mg Tablet (14-27/Corr.) **ii.** Primaquine 15mg Tablets (28-33/Corr.)
15	Summary of Protocol	Attached.

16	Summary of Investigator Brochure	Not applicable as both IMPs are registered & PIL are provided: **iii.** Kodatef ® (Tafenoquine Succinate) 100mg Tablet (14-27/Corr.) **iv.** Primaquine 15mg Tablets (28-33/Corr.)
17	Adverse Event Reporting Form	Not provided.
18	No of patients to be enrolled in each center.	960 participants (Globally) as per US Trial Registry 720 participants (Globally) as per application & 240 participants in Pakistan.
19	Name of Monitors & Clinical Research Associate	Not provided.
20	Evidence of registration in country of origin.	**Not provided.** GMP Certificate(s) of following IMPs manufacturer(s) are attached: vi. M/s The Government Pharmaceutical Organization, Thailand. vii. M/s Piramal Pharma Limited, India. CoPP/Free Sale Certificate(s) of following IMPs are attached: ii. Primaquine 15mg Tablets manufactured by M/s The Government Pharmaceutical Organization, Thailand. * CoPP/Free Sale Certificate for Kodatef (Tafenoquine as succinate) 100mg Tablets manufactured by M/s Piramal Pharma Limited, India, or GMP Certificate of M/s Biocelect Pty Ltd., Australia need to be provided & it should be clarified that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the applied Clinical Trial.
21	Copy of registration letter (if registered in Pakistan)	**Not applicable.**
22	Sample of label of the investigational product / drug.	Attached but not as per ICH-GCP Guidelines, IMPs label should contain following statement: *For Investigational Use only*.
22	Duration of trial	Individual trial duration approximately 6 months Total trial duration is estimated to 24 months.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings are recorded:

i. In study objective in Pakistan are not described as mentioned for other countries in provided protocol.
ii. Details regarding trial subject(s) insurance in Pakistan is not provided.
iii. Anticipated cost of the project has not been informed.
iv. It is mentioned in the Informed Consent Form that, "*The study cannot compensate you or pay for life-long or long-term care for study related injuries or for any long-term ill effects to your health*". It needs to be clarified as ethically trial associated injuries/health issues should be covered in trial subject insurance.
v. As per U.S. trial registry there are 960 participants (Globally) for the trial. Whereas in the application 720 participants (Globally) & 240 participants will be enrolled in Pakistan. Clarification need to be provided for difference in trial subjects.
vi. Justification for IMPs quantity need to be imported for the CT as per number of subject(s), dosing & surplus quantity/retention sample, need to be provided.
vii. Following proposed CTS are not approved:
    a. Khidmat-e-Alam Medical center, Nazimabad, Pakistan.
    b. Thatta Civil Hospital, Thatta, Sindh province, Pakistan.
viii. None of PI/Co-PI are involved from proposed Clinical Trial Site(s).

ix. CoPP/Free Sale Certificate for Kodatef (Tafenoquine as succinate) 100mg Tablets manufactured by M/s Piramal Pharma Limited, India, or GMP Certificate of M/s Biocelect Pty Ltd., Australia, need to be provided & it should be clarified that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the applied Clinical Trial.

x. Sample label is attached but not as per ICH-GCP Guidelines, IMPs label should contain following statement:

   a. *For Investigational Use only.*

06. In the view of above, shortcomings communicated to applicant/PI for fulfillments on 30th August, 2022 but still response 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. Dr. Ali Faisal Saleem, Associate Professor, Vice Chair - Clinical Services, Department of Pediatrics & Child Health – MC, Director. Infectious Diseases Research Laboratory, Aga Khan University Hospital, Stadium Road, Karachi, in response to CSC decision submitted following reply, which was received on 27th October, 2022.

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

Sr.	Descriptions / Shortcomings	Reply	Remarks
01	In study objective in Pakistan is not described as mentioned for other countries in provided protocol.	This is an international multi-center trial so the study objectives are standardized for all sites.	---

02	Details regarding trial subject(s) insurance in Pakistan is not provided.	Yes, trial has insurance cover and letter is attached for reference. Insurance is renewed every year by sponsor so updated letter would be provided once renewed (Page 528-529/Corr.)	---
03	Anticipated cost of the project has not been informed.	The estimated cost of the project is $ 404,771.	---
04	It is mentioned in the Informed Consent Form that, "*The study cannot compensate you or pay for life-long or long-term care for study related injuries or for any long-term ill effects to your health*". It needs to be clarified as ethically trial associated injuries/health issues should be covered in trial subject insurance.	Recommended changes have been made to the consent forms and the clause has been deleted and submitted to the NBC and the ERC.	---
05	As per U.S. trial registry there are 960 participants (Globally) for the trial. Whereas in the application 720 participants (Globally) & 240 participants will be enrolled in Pakistan. Clarification need to be provided for difference in trial subjects.	The total number of participants is indeed 960. It was 720 before Pakistan was added. So, this information has been added to the protocol and the amended protocol has been submitted to the NBC and ERC.	---
06	Justification for IMPs quantity need to be imported for the CT as per number of subject(s), dosing & surplus quantity/retention sample, need to be provided.	The quantities have been calculated based on the dosing mentioned in the protocol i.e. the number of the tablets per arm for both the Primaquine and the Tafenoquine. The considered sample size is 80 participants each arm. It is to notify that we have calculated the dosing in accordance with the dosing of the weight more than 70 kg (mentioned in protocol) just to assure the ample quantity in hand during the trial as weight among patients is uncertain. For the Primaquine we have requested to import approximately 40% of the excess medication than the required amount as this would be required in two arms and has scheduled dosing of 7 and l4 days in both PQ7 and PQl4 arms respectively. 25% of the excess is because of the anticipated relapses and the l5% of the excess quantity is to cover the wastage of the medication from the patient's side and any unforeseeable damage to medications. In case of Tafenoquine the excess quantity is approximately 25% excess than the required quantity, quantity is less considering the fact that it requires single dose, half of that excess would be for relapses and half of it would be for the wastage from patient side.	---
07	Following proposed CTS are not approved: a. Khidmat-e-Alam Medical center, Nazimabad, Pakistan. b. Thatta Civil Hospital, Thatta, Sindh province, Pakistan.	These are not the Clinical Trial sites for the concerned Project. They will be referral centers. The Clinical Trial Site is Aga Khan University where the potential participants will be referred. The amendments regarding this have been made and the revised protocols have been shared with the ERC and NBC and approval is awaited.	Following AKUH IRB/ERC approval/ amendment are attached: **i.** Approval letter No. Nil, dated 05th August, 2022 for a period of one year is attached. **ii.** Approval letter No. Nil, dated 15th September, 2022. **iii.** Approval letter No. Nil, dated 30th September, 2022. Following NBC approval/amendment letters are attached: i. Ref: No.4-87/NBC-772/22/125, dated 10th August, 2022. (Study Approval) for a period of one year.

			ii. Ref: No.4-87/NBC-772/22/330, dated 13th September, 2022 (Change in Clinical Trial Sites) ii. Ref: No.4-87/NBC-772 / 22/543, dated 25th October, 2022 (Increase in sample size from 720-960 subjects).
08	None of PI/Co-PI are involved from proposed Clinical trial Site(s).	Khidmat-e-Alam und Thatta Civil Hospital are the referral centers. These centers will only refer potential subjects to Aga Khan University so, there will not be such involvement of the referral physicians hence, the CO-PI and the PI ore from main Clinical Trial Site i.e. Aga Khan University .	---
09	CoPP/Free Sale Certificate for Kodatef (Tafenoquine as succinate) 100mg Tablets manufactured by M/s Piramal Pharma Limited, India, or GMP Certificate of M/s Biocelect Pty Ltd., Australia, need to be provided & it should be clarified that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the applied Clinical Trial.	We have discussed this with Biocelect, and following justification has been provided by them: The GMP certificate lists the manufacturer and the manufacturing site - as such the clearance is issued to Piramal (not to Biocelect). They submit these GMP certificates which list the manufacturer to the TGA. These certificates will never contain Biocelect details.	Kindly clarify that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the trial. If the tablets are manufactured by M/s Biocelect Pty Ltd., Australia & imported for this trial from Australia then requirements are fulfilled. Otherwise, if the tablets are manufactured by M/s Piramal Pharma, India, then toll manufacturing agreement along with CoPP issued to M/s Piramal Pharma, India need to be provided.
10	Sample label is attached but not as per ICH-GCP Guidelines, IMPs label should contain following statement: a. *For Investigational Use only.*	The medications are labelled prior dispensing by CTU pharmacist in accordance with the ICH-GCP guidelines. The sample is attached for your reference. (Page 424/Corr.)	---

10. After evaluation following shortcoming/clarification need to be provided:

i. After evaluation clarification required that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the trial (Australia or India). If the Kodatef Tablets are manufactured by M/s Biocelect Pty Ltd., Australia & imported for from Australia then requirements are fulfilled. Otherwise, if the tablets are manufactured by M/s Piramal Pharma, India, then toll manufacturing agreement along with CoPP issued to M/s Piramal Pharma, India need to be provided.

11. Secretary CSC presented the case before CSC. Dr. Muhammad Asim (PI) also joined the meeting through Zoom, CSC members raised several queries with respect to the matter in vogue but PI failed to satisfy, since he had no convincing answer regarding the IMPs origin. 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. After evaluation clarification required that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the trial (Australia or India). If the Kodatef Tablets are manufactured by M/s Biocelect Pty Ltd., Australia & imported for from Australia then requirements are fulfilled.

Otherwise, if the tablets are manufactured by M/s Piramal Pharma, India, then toll manufacturing agreement along with CoPP issued to M/s Piramal Pharma, India 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.

AGENDA ITEM VIII:

APPLICATION FOR REGISTRATION AND APPROVAL OF CLINICAL TRIAL TITLED "IMMUNOGEENICITY OF NOVEL ORAL POLIOMYELITIS VACCINE TYPE 2 (nOPV2) IN HEALTHV CHILDREN AGED 1- 15 YEARS IN SETTINGS AT HISH RISK OF cVDPV2 OUTBREAKS", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-19/2022-DD (PS)

Application is from Dr. Ali Faisal Saleem (CNIC 42201-0534184-9), Associate Professor, Vice Chair - Clinical Services, Department of Pediatrics & Child Health – MC, Director. Infectious Diseases Research Laboratory, Aga Khan University Hospital, Stadium Road, Karachi dated 29th August, 2022, wherein request has been made for approval of subject 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.200000/- deposited vide challan number: 9650965016, dated 12th August, 2022.

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

i. **Sponsor:** Global Polio Eradication Initiative (GPEI)
ii. Collaborators;
   a. National Emergency Operations Center, Pakistan.
   b. National Institute of Health, Pakistan.
   c. Centers for Disease Control and Prevention, USA

iii. Purpose/background of trial: The Global Commission for the Certification of Poliomyelitis Eradication (GCC) declared worldwide eradication of wild type 2 poliovirus (WPV2) in2015. However, continued used of trivalent oral polio vaccine (tOPV) posed an on-going risk of circulating vaccine-derived poliovirus 2 (cVDPV2) and vaccine-associated paralytic poliomyelitis (VAPP), due to the small chance of neurovirulence. Therefore, all countries using oral polio vaccine switched to bivalent oral polio vaccine (bOPV2) without type 2 strain in 2016. This has resulted in waning immunity for polio type 2 over the years. Current outbreak control measures include the use of monovalent sabin oral poliovirus vaccine type 2 (mOPV2). However, the use sabin moPV2 for cVDPV2 outbreak control has led to further seeding of cVDPV2 outbreaks, with approximately 1048 cases of cVDPV2 reported in2020 from 33 countries.

The novel OPV2 (nOPV2) was developed with the intention of having an OPV with increased genetic stability, thereby reducing the possibility of seeding VDPV. The nOPV2 has been clinically tested in randomized control trials among adults in Belgium and among infants and children in Panama and found to be safe and immunogenic. The nOPV2 received recommendation under the WHO Emergency Use Listing (EUL) procedure in November 2020, for use in vaccination campaigns as part of response to cVDPV2 outbreaks.

Mass polio vaccination campaigns traditionally target children under 5 years of age, the primary age group that reports poliomyelitis and is responsible for highest proportion of transmission. However, as intestinal immunity to poliovirus wanes over time, individuals previously vaccinated with oral poliovirus vaccine (OPV) can become re-infected and shed poliovirus. Whilst cases of poliomyelitis among older children and adults are rare, infection in this group can contribute to sustained transmission. There is clinical data demonstrating the ability of OPV and IPV to boost mucosal and humoral immunity in older children that have previously been vaccinated or exposed to circulating

virus. The strategy of expanding the age range of outbreak response vaccination campaigns with Sabin OPV has been implemented in some circumstances, such as in Tajikistan and Namibia.

The new GPEI strategic plan proposes expanding the age range of mass vaccination campaigns in high-risk areas. Therefore, it is necessary to evaluate the ability of nOPV2 to boost mucosal and humoral immunity in older children in high-risk areas. This study aims generate data on the immunogenicity of one and two doses of nOPV2 in high-risk polio settings such as Pakistan in children in an expanded age range. The secondary objective will assess nOPV2's ability to induce mucosal immunity expressed by the reduction in shedding of the vaccine virus after the 2nd nOPV2 dose. ln addition, baseline blood sample and shedding after the 1st nOVP2 dose will provide an insight into the current humoral and mucosal immunity in older children in high-risk areas.

iv. Role of Partners

- **WHO** will provide funding for the successful implementation of the study, provide technical support and oversight, conduct analyses of the study results, support the development of conference abstract(s) and manuscript(s).

- **Aga Khan University** will provide scientific leadership, recruit study team members (e.g., data collectors, data entry and analyst, nurses and/or lab technicians etc.) develop the sampling frame, conduct training workshop, conduct field activities, support the development of conference abstract(s) and manuscript(s), generate and submit final report and disseminate reports to the Liberian MoH and partners, etc.

- **NIH Pakistan** will conduct the laboratory analyses of blood and stool samples.

v. Source of Investigational Medical Products (IMPs):

a. NOVEL ORAL POLIOMYELITIS VACCINE TYPE 2 (NOPV2); Drops; Box, 10 vials @ 5 ml (50 doses) manufactured by M/s PT. BIO FARMA, Jl. Pasteur No. 28 Bandung 40161 – Indonesia.

vi. Number of subjects to be recruited: 525 Subjects (Children's) in Pakistan.

vii. Anticipated cost of the project: USD 151,556/-

viii. Study design & details:

a. Cross-Sectional Survey

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

A. Primary Objective: To determine the immunogenicity of one and two doses of nOPV2 in healthy children aged 1- 15 years in settings at high risk of cVDPV2 outbreaks.

B. Secondary Objectives: To assess nOPV2's ability to induce mucosal immunity in children aged 1- 15 years, expressed by the reduction in shedding of the vaccine virus after the 2nd nOPV2 dose.

C. Endpoints: Seroconversion will be defined as a change from seronegative (reciprocal titer <8) to seropositive (reciprocal titer >= 8) for subjects with no detectable antibody titers at baseline OR a four-fold rise in antibody titres over the expected decline of maternal antibodies.

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.200000/- deposited vide challan number: 9650965016, dated 12th August, 2022. * Original challan (DRAP's Copy) need to be provided.
3	Investigator Brochure (s)	Patient Information Leaflet is attached, as IMP is registered.
4	Final protocol	Attached Protocol No. nOPV2Pak2022v4 Version V4_31032022.

		* Protocol is not as per ICH-GCP Guidelines. ** There is no detail regarding insurance of study subjects. *** As per mentioned role of NIH, Islamabad, no evident document is attached for NIH approval as a Bio-Analytical Laboratory for Clinical Trials from DRAP.
5	Informed consent and participant information sheet (Urdu to English)	Attached I English only. * There is no detail regarding insurance of study subjects.
6	List of participating countries	Pakistan only.
7	Phase of trial.	Phase – IV
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Total 525 Children's will be enrolled in the study & each child will be given two doses of nOPV2. Therefore 30 vials of 50 doses each (1500 doses) will be required.
9	Site of the trial	Clinical Trial Unit, Aga Khan University Hospital, Karachi. • Bin-Qasim town (Cattle colony) • Ali Akbar Shah • Rehri Goth and extension area • Ibrahim Hyderi and extension area Mentioned Study sites/areas are not approved from DRAP.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Approval reference letter No. Nil, dated 22nd October, 2021 is attached (for a period of **one** year). * As IRB approval is near to its expiry, fresh IRB approval need to be provided.
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter No. 4-87/NBC-693/21/724, dated 05th November, 2021 & 4-87/NBC-693/22/1636, dated 08th March, 2022 (for a period of **One** year) (Amendment) is attached.
12	CV's of the Investigators	CVs of following experts are attached. **ix.** Dr. Ali Faisal Saleem (PI) (59-66/Corr.) **x.** Dr. Zaubina Umar Kazi (Co-PI) (67-69/Corr.)
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Certificate of Pharmaceutical Product of following is attached: viii. NOVEL ORAL POLIOMYELITIS VACCINE TYPE 2 (NOPV2); Drops; Box, 10 vials @ 5 mL (50 doses) GMP Certificate of the manufacturer is not provided: i. M/s PT. BIO FARMA, Jl. Pasteur No. 28 Bandung 40161 – Indonesia.
14	Pre-clinical/clinical safety studies	Not provided. Available Preclinical & Clinical Data need to be provided.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	As product is registered in the country of origin so not applicable.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	525 Subjects (Children's) in Pakistan.
19	Name of Monitors & Clinical Research Associate	--
20	Evidence of registration in country of origin.	Certificate of Pharmaceutical Product of following is attached:

		i. NOVEL ORAL POLIOMYELITIS VACCINE TYPE 2 (NOPV2); Drops; Box, 10 vials @ 5 mL (50 doses)
21	Copy of registration letter (if registered in Pakistan)	**Not applicable.**
22	Sample of label of the investigational product / drug.	Attached. But IMPs label should contains following statement: *For Investigational Use only.*
22	Duration of trial	12 Months. This includes 6 months for data collection and the remaining 6 months for data entry, cleaning, analysis, and dissemination.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings are recorded:

i. Original fee challan (DRAP's Copy) is not provided.
ii. Following study sites/areas mentioned in the application are not approved from DRAP
    a. Bin-Qasim town (Cattle colony)
    b. Ali Akbar Shah
    c. Rehri Goth and extension area
    d. Ibrahim Hyderi and extension area
iii. Attached protocol is not as per ICH-GCP Guidelines.
iv. There is no detail regarding insurance of study subjects in Protocol and in the Informed Consent Form.
v. As per mentioned role of NIH, Islamabad, no evident document is attached for NIH approval as a Bio-Analytical Laboratory for Clinical Trials from DRAP.
vi. In attached protocol (Annex-1, Consent Form) it is mentioned that, blood samples will be stored at -800°C at AKUH-Infectious Diseases Research Laboratory (IDRL)but there is no freezer available with this range.
vii. Approval reference letter No. Nil, dated 22nd October, 2021 is attached (for a period of **one** year). As IRB approval is near to its expiry, fresh IRB approval need to be provided.
viii. GMP Certificate of the manufacturer M/s PT. BIO FARMA, Jl. Pasteur No. 28 Bandung 40161 – Indonesia, is not provided.
ix. Pre-Clinical/Clinical data is not provided. Available Preclinical & Clinical Data need to be provided.
x. Sample label for IMPs is attached. Further, IMPs label(s) should contain following statement:
    a. *For Investigational Use only.*

06. Accordingly, shortcomings have been communicated vide letter bearing even number dated 29th September, 2022 but still response is awaited.

07. The application was placed before CSC in its 35th meeting & 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. Original fee challan (DRAP's Copy) is not provided.
ii. Following study sites/areas mentioned in the application are not approved from DRAP
    a. Bin-Qasim town (Cattle colony)
    b. Ali Akbar Shah
    c. Rehri Goth and extension area
    d. Ibrahim Hyderi and extension area
iii. Attached protocol is not as per ICH-GCP Guidelines.
iv. There is no detail regarding insurance of study subjects in Protocol and in the Informed Consent Form.
v. As per mentioned role of NIH, Islamabad, no evident document is attached for NIH approval as a Bio-Analytical Laboratory for Clinical Trials from DRAP.

vi. In attached protocol (Annex-1, Consent Form) it is mentioned that, blood samples will be stored at -800°C at AKUH-Infectious Diseases Research Laboratory (IDRL)but there is no freezer available with this range.
vii. Approval reference letter No. Nil, dated 22nd October, 2021 is attached (for a period of **one** year). As IRB approval is near to its expiry, fresh IRB approval need to be provided.
viii. GMP Certificate of the manufacturer M/s PT. BIO FARMA, Jl. Pasteur No. 28 Bandung 40161 – Indonesia, is not provided.
ix. Pre-Clinical/Clinical data is not provided. Available Preclinical & Clinical Data need to be provided.
x. Sample label for IMPs is attached. Further, IMPs label(s) should contain following statement:
b. *For Investigational Use only.*

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

8. Accordingly decision of the Committee was communicated on 14th October, 2022. Applicant/ PI, Dr. Ali Faisal Saleem, Associate Professor, Vice Chair - Clinical Services, Department of Pediatrics & Child Health – MC, Director. Infectious Diseases Research Laboratory, Aga Khan University Hospital, Stadium Road, Karachi, submitted reply in response to CSC decision which was received on 27th October, 2022.

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

Sr.	Descriptions / Shortcomings	Reply	Remarks
01	Original fee challan (DRAP's Copy) is not provided.	Original fee Challan attached (Annexure 1) Page 109/Corr.	---
02	Following study sites/areas mentioned in the application are not approved from DRAP a. Bin-Qasim town (Cattle colony) b. Ali Akbar Shah c. Rehri Goth and extension area d. Ibrahim Hyderi and extension area	The participant pool will be derived from the 4 peri-urban sites through a Demographic Surveillance System which is already in place. The list will be used to by the study staff to identify and enlist eligible children. Evaluation will be done to see whether the child meets the eligibility criteria for inclusion into the study. Potentially eligible children will be brought to the CTU at Aga Khan University Hospital and will be screened to determine if they fit into the study criteria. Eligible participants will be enrolled in the study at CTU. Consequent study sampling and vaccine administration will also be done at the CTU.	---
03	Attached protocol is not as per ICH-GCP Guidelines.	Protocol changed according to the ICH-GCP Guidelines. (Annexure 2) Page 110-142/Corr.	Protocol Identifying Number: 2021-6410 - 19648 Dated 20th October, 2022.
04	There is no detail regarding insurance of study subjects in Protocol and in the Informed Consent Form.	Letter from insurance company is attached. (Annexure 3) Page 144/Corr.	---
05	As per mentioned role of NIH, Islamabad, no evident document is attached for NIH approval as a Bio-	Collaboration letter attached. (Annexure 4) Page 146/Corr.	As per the Bio-Study Rules, 2017 NIH, Islamabad is not an approved Bio-

	Analytical Laboratory for Clinical Trials from DRAP.		Analytical Laboratory for Clinical Trials.
06	In attached protocol (Annex-1, Consent Form) it is mentioned that, blood samples will be stored at -800°C at AKUH-Infectious Diseases Research Laboratory (IDRL)but there is no freezer available with this range.	Typo Error, it was -800C	---
07	Approval reference letter No. Nil, dated 22nd October, 2021 is attached (for a period of **one** year). As IRB approval is near to its expiry, fresh IRB approval need to be provided.	IRB extension is attached. (Annexure 5) Page 148/Corr.	---
08	GMP Certificate of the manufacturer M/s PT. BIO FARMA, Jl. Pasteur No. 28 Bandung 40161 – Indonesia, is not provided.	Attached (Annexure 6)	---
	Pre-Clinical/Clinical data is not provided. Available Preclinical & Clinical Data need to be provided.	Reference Studies are attached. (Annexure 7)	---
	Sample label for IMPs is attached. Further, IMPs label(s) should contain following statement: a. *For Investigational Use only.*	Picture & email attached. (Annexure 8)	---

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

Decision:

The CSC after detailed discussion and deliberation decided to approve the Phase-IV Clinical Trial titled, "Immunogenicity of Novel Oral Poliomyelitis Vaccine Type 2 (nOPV2) in Healthy Children Aged 1- 15 Years in Settings at High Risk of cVDPV2 Outbreaks", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Sites:

i. CTU, Aga Khan University Hospital, Stadium Road, Karachi, Sindh.

A total of 525 Children's will be enrolled in the study & each child will be given two doses of nOPV2. Therefore 30 vials of 50 doses each (1500 doses) will be required and trial complete duration will be 12 Months. (This includes 6 months for data collection and the remaining 6 months for data entry, cleaning, analysis, and dissemination.)

AGENDA ITEM IX:

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** Chairman CSC/Director, Division of Pharmacy Services-DRAP.
ii.	**Prof. Dr. Nisar Hussain Shah** Dean Faculty of Pharmacy, Bahauddin Zakariya University, Multan
iii.	**Prof. Dr. Ali Jawa** University of Health Sciences, Lahore.
iv.	**Dr. Farhana Badar** Biostatistician, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.
v.	**Shafqat Hussain Danish** 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. Secretary CSC presented the case before CSC & 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.

AGENDA ITEM X:

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)	Phase-II

	2. Nitazoxanide (500 mg tablet) (Trade Name: IZATO) 3. Molnupravir (200 mg Capsule) (Trade Name: MONUVIR) 4. Nirmatrevir/ritonavir (Nirmatrevir 150 mg tablet; Ritonavir: 100 mg tablet) (Trade Name: PAXOVIR) 5. Fluoxetine (20 mg tablet) (Trade Name: FLUX) 6. Ensitrelvir (Each tablet contains Ensitrelvir fumaric acid 125 mg). 7. B REGN-COV2 (600 mg Casirivimab/600 mg Imdevimab) 8. Sotrovimab (500 mg /8 ml) 9. A combination of Molnupiravir and Nirmatrevir/ritonavir (Trade Name: MONUVIR and PAXOVIR) L0. Evusheld (150 mg of the tixagevimab and 150 mg of the Cligavimab)	

vi. **Arms & Interventions:**

Arms	Intervention/treatment
Active Comparator: Positive control (monoclonals)	Drug: Monoclonal antibodies Monoclonal antibodies: 600mg casirivimab/ 600mg imdevimab given once on D0
Experimental: Favipiravir	Drug: Favipiravir Favipiravir 1800mg BD D0 and 800mg BD for a further 6/7.
Experimental: Ivermectin [This arm is now closed to recruitment]	Drug: Ivermectin Ivermectin 600micrograms/kg/day for 7/7.
Experimental: Remdesivir [This arm is now closed to recruitment]	Drug: Remdesivir Remdesivir 200mg D0 and 100mg for a further 4/7.
Negative control group	Other: No treatment No treatment (except antipyretics- paracetamol)
Experimental: Fluoxetine	Drug: Fluoxetine Fluoxetine 40mg OD for 7/7
Experimental: Molnupiravir	Drug: Molnupiravir Molnupiravir 800mg BD for 5/7
Experimental: Nirmatrelvir/ritonavir (e.g. PAXLOVID™)	Drug: Nirmatrelvir/ritonavir (e.g. PAXLOVID™) Nirmatrelvir 300mg BD for 5/7 Ritonavir 100mg BD for 5/7
Experimental: Nitazoxanide	Drug: Nitazoxanide 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: **iii.** Paxovir (Nirmatrevir 150 mg & Ritonavir: 100 mg) Tablets (17/Corr.) **iv.** Monuvir (Molnupravir) Capsules Mfg:by ESKYEF Pharma Bangladesh (18/Corr.). **v.** FAVUZA (Favipiravir 200 mg) Mfg:by Sami Pharma, Pakistan (19/Corr.) **vi.** Izato (Nitazoxanide) 500 mg tablet Mfg:by Sami Pharma, Pakistan (21/Corr.) **vii.** Flux (Fluoxetine 20 mg tablet) Mfg: By Hilton Pharma, Pakistan. (22-23/Corr.) **viii.** Xocova (Ensitrelvir fumaric acid 125 mg) Tablets Mfg: By Shionogi & Co., Ltd. Japan (24-30/Corr.) **ix.** Xevudy (Sotrovimab) 500 mg /8 ml concentrated solution for infusion Mfg: By GlaxoSmithKline, UK (208-217/Corr.) **Investigators Brochure** of following IMPs is attached: i. S-217622, Mfg: By Shionogi Inc., USA. (31-207/Corr.) * IB/PIL of following IMPs are not provided. i. Hydroxychloroquine ii. Remdesivir

		iii. Lopinavir/Ritonavir iv. Miglustat v. Ivermectin vi. REGN-COV2 with Casirivimab & Imdevimab) vii. Nebulized Unfractionated Heparin viii. Fluvoxamine ix. AZD7442 (Evusheld) ** Clarification required that, why different origin IMPs are utilized in a MRCT. *** 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 Protocol No. VIR21001 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. * Some are unconfirmed sites.
7	Phase of trial.	Phase – II * 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: 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
9	Site of the trial	M/s Aga Khan University Hospital, Karachi. * 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	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.

	committee i.e. names and designation of members.	
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. **xi.** Dr. Muhammad Asim Beg (PI) (AKUH)(308-337/Corr.) **xii.** Dr. Farah Naz Qamar (Co-PI) (400-412/Corr.) **xiii.** Dr. Abdul Momin Kazi (Co-PI) (358-383/Corr.) **xiv.** Dr. Syed Faisal Mahmood (Co-Investigator) (338-347/Corr.) **xv.** Dr. Najia Bano Ghanchi (Ph.D. Biotechnology) (Co-Investigator) (384-398/Corr.) **xvi.** Dr. Aisha Ilyas (Co-Investigator) (414-416/Corr.) **xvii.** 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: i. M/s SAMI Pharmaceuticals (Pvt.) Ltd., Karachi. ii. M/s ESKAYEF Pharmaceuticals Ltd., Gazipur, Bangladesh iii. M/s Hilton Pharma (Pvt.) Ltd., Karachi. iv. M/s Shionogi Pharma Co., Ltd., Osaka, Japan (For S-217622 IMPs) CoPP/ Registration Certificates of following manufacturer(s) are provided: v. FAVUZA (Favipiravir 200mg) Tablets. vi. IZATO (Nitazoxanide 500mg) Tablets. vii. MONUVIR (Molnupravir 200 mg) Capsule (CoPP for Ukraine is attached) viii. PAXOVIR (Nirmatrevir150 mg) tablet (CoPP for Ukraine is attached) ix. FLUX (Fluoxetine 20 mg) Total 840 Tablets (Registration letter of FLUX 20mg Capsules is attached instead of Tablets) 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) COA is attached for following: xi. S-217622 IMPs GMP Certificate of following are not provided: i. M/s Roche Registration GmbH, Germany. ii. M/s GENENTECH Inc., Hillsboro, Oregon, USA. iii. Manufacturer of Ritonavir 100mg tablet iv. Manufacturer of Ensitrelvir fumaric acid 125 mg v. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion

		vi. Any other manufacturer whom IMPs details not attached with dossier. CoPP of the following are not provided: i. Ritonavir 100mg tablet ii. Ensitrelvir fumaric acid 125 mg iii. Sotrovimab (500 mg/8 ml) Infusion iv. Evusheld Tixagevimab 150mg & Cligavimab 150mg) 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 1250 subjects from Brazil, Thailand, Laos & other two countries (Yet unconfirmed) 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: **i.** FAVUZA (Favipiravir 200 mg) Mfg:by Sami Pharma, Pakistan (578 & 583/Corr.) **ii.** Izato (Nitazoxanide) 500 mg tablet Mfg:by Sami Pharma, Pakistan (579/Corr.) **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.) **v.** Paxovir (Nirmatrevir 150 mg & Ritonavir: 100 mg) Tablets Mfg:by ESKYEF Pharma Bangladesh (602-603/Corr.). **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.). * 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: **i.** FAVUZA (Favipiravir 200 mg) Mfg:by Sami Pharma, Pakistan (578 & 583/Corr.) **ii.** Izato (Nitazoxanide) 500 mg tablet Mfg:by Sami Pharma, Pakistan (579/Corr.) **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.) * 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
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. 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. 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. The US trial Registry Clintrials.gov contains all the drugs which we are currently assessing or have assessed in Thailand and Brazil. We 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.	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.
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. a. Hydroxychloroquine b. Remdesivir	a) Hydroxychloroquine (Not part of Pakistan Protocol) b) Remdesivir (Not part of Pakistan Protocol) c) Lopinavir/Ritonavir (Not part of Pakistan Protocol) d) Miglustat (Not part of Pakistan Protocol) e) Ivermectin (Not part of Pakistan Protocol)	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

	c. Lopinavir/Ritonavir d. Miglustat e. Ivermectin f. REGN-COV2 with Casirivimab & Imdevimab) g. Nebulized Unfractionated Heparin h. Fluvoxamine i. AZD7442 (Evusheld)	f) Nebulized Unfractionated Heparin (Not part of Pakistan Protocol) g) Fluvoxamine (Not part of Pakistan Protocol) h) REGN-COV2 with Casirivimab and Imdevimab, Thank you. We have attached the Patient Information Sheet. i) AZD7442 (Evusheld). Already shared with the initial application (Refer to the initial application dated 15/09/2022)	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
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 submitted that, where theses assay/tests will be conducted.	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 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: 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.	a) M/s Roche Registration GmbH Germany. (The medication will not be procured from this pharmaceutical) b) M/s GENETECH Inc. Hillsboro, Oregon, USA (GMP Shared) c) Manufacturer of Ritonavir 100mg tablet (GMP shared) d) Manufacturer of Ensitrelvir fumaric acid 125mg (GMP Shared) e) GlaxoSmithKline, UK manufacturer of Sotrovimab (500mg /8 ml) infusion f) Any other manufacturer whose IMPs details are not attached with dossier 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): i. Manufacturer of Ensitrelvir fumaric acid 125 mg ii. GlaxoSmithKline, UK Manufacturer of Sotrovimab (500 mg/8 ml) Infusion iii. Any other manufacturer whom IMPs details not attached with dossier.
09	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.	a) Ritonavir 100mg tablet, The CoPP is shared as it is a combination medication or Nirmatrelvir/ Ritonavir b) Ensitrelvir fumaric acid 125mg, Certificate of Analysis is provided. c) Sotrovimab (500mg /8 ml) infusion d) Evusheld Tixagevimab 150 mg & Cligavimab 150mg e) CoPP of other IMPs Which is not included in the list with dossier 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: i. Ensitrelvir fumaric acid 125 mg ii. Sotrovimab (500 mg/8 ml) Infusion iii. Evusheld Tixagevimab 150mg & Cligavimab 150mg) iv. CoPP of other IMPs as mentioned in the protocol, which are not included in the list with dossier need to be provided.
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 Authority and to the local Ethics Committee and other parties as applicable. 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. 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 able to determine differences related to drugs of different origins in the study.	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.

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
01	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.	This is correct - we are trying to attain the requisite 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.	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.

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: 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	Thank you, we have attached the amended protocol that reflects the IMPs that will be used by the AKU Pakistan site. (Page 872-932/Corr.)	Following IMPs are mentioned in schedule 16 as follows: 16.1 Nitazoxanide 16.2 REGN-COV2 16.3 Not mentioned. 16.4 Not mentioned. 16.5 Not mentioned. 16.6 Not mentioned. 16.7 Not mentioned. 16.8 Favipiravir 16.9 Molnupiravir 16.10 Nirmatrelvir/ritonavir (e.g. PAXLOVID™) 16.11 Fluoxetine 16.12 Ensitrelvir 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. (Page 933-934/Corr.)	AKUH-IRB/ERC approval dated 15th November, 2022 is attached 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 along with SOPs for PK/PD sampling & its shipment, needs to be provided as described in the protocol section 7.9 of protocol.	Thank you we have attached the SOPs for PK/PD sampling and Shipment. The need for an MTA with 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. (Page 936-940/Corr.)	Un-signed draft MTA for PK/PD Studies between Mahidol Oxford Tropical Medicine Research Unit & 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): 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.	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	Since the drug is in an investigational phase, CoPP is	---

	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.	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. (935/Corr.)	---

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. Secretary CSC presented the case before CSC. Dr. Muhammad Asim (PI) also joined the meeting through Zoom, CSC members raised several queries with respect to the matter in vogue but PI failed to satisfy. 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. 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.

AGENDA ITEM XI:

APPLICATION FOR APPROVAL OF 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 is from Dr. M.A. Rehman Siddiqui, CNIC number: 42101-11743608-3, PI of applied trial, The Aga Khan University Hospital, Karachi, Pakistan, Stadium Road, Karachi, received on 21st October, 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. 566016616739, dated 11th October, 2022. The trial is also enlisted on U.S National Trial Registry with identification number ***NCT05155293*** *(https://www.clinicaltrials.gov/ct2/show/NCT05155293)*

2. The details regarding trial are as under:

i. **Sponsor & Responsible Party:** Alvotech Swiss AG, Switzerland.

ii. **Contact information:** Stephanie Koelbl +4915128088914 stephanie.koelbl@alvotech.com
Sara Marques +41798338839 sara.marques@alvotech.com

iii. Purpose of trial: This study aims to demonstrate equivalent efficacy of AVT06 to Eylea. The sample size calculation is based on the primary efficacy endpoint of change in BCVA as assessed by ETDRS letter score from baseline to Week 8 with an equivalence margin between the AVT06 and Eylea of [-3.5 to 3.51. The primary endpoint will be analyzed based on the Full Analysis Set (FAS) according to randomized study treatment excluding subjects with intercurrent events (ICE) that can lead to attenuation of the difference between the treatment groups. The primary endpoint will be analyzed using a mixed model for repeated measures adjusting for baseline BCVA and geographical origin. An unstructured covariance structure will be used to model the within subject error and an adjustment to the degrees of freedom will be made using the Kenward-Roger's approximation. At Week 8, the least square (LS) means by treatment group and difference between treatment groups will be provided together with two-sided 95% confidence interval (CI) (as required by the European Medicines Agency) and two-sided90% Cl (as required by the Food and Drug Administration) for the difference. If these CIs are completely contained within the prespecified equivalence margin of [-3.5 to 3.5], an efficacy equivalence can be demonstrated respectively. Further sensitivity analysis will be undertaken based on the FAS and using the estimands framework for different ICE strategy. All statistical analysis will be performed using SAS® statistical software (version 9.4 or higher). For the secondary endpoints, all results will be interpreted descriptively for the 2 treatment groups and for each study visit time points. Safety data will be summarized and listed based on the Safety Analysis Set (SAF). Immunogenicity data will be summarized and listed based on the SAF. Serum concentrations of free and bound aflibercept will be listed and summarized, based on the Pharmacokinetic

Analysis Set. The maximum observed concentration (Cmax) and time to Cmax (Tmax) of free and bound aflibercept will be determined.

iv. Bioanalytical Assays:

Bioanalytical & testing for the subject trial will be carried out by Q^2 Solutions Pte. Limited, Singapore. Material Transfer Agreement between Aga Khan University & the Q^2 Solution on behalf of Sponsor is provided. (Page 774-778/Corr.)

v. Justification regarding Investigational Medical Products (IMPs) & Quantity:

INN	Strength	Quantity
International Nonproprietary Names (INN): Aflibercept Brand name EU Eylea or INN AVT06	In the study eye subjects will receive 2 mg (0.05 ml) intravitreal injection of AVT06 or Eylea (Dosage Formulation: 40 mg/ml) 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).	28 healthy volunteers over 6 sites (Competitive enrollment) + 25% overage:140/140 (names of trial sites mentioned in clause 11)

IMP	Active	Strength	Packing Size	Total Quantity
AVT06	(Dimeric Glycosylated recombinant fusion glycoprotein)	40 mg/ml Dosage Formulation: 2 mg (0.05 mL) – Unit Dose Strength(s)	AVT06 will be provided as single-dose vials. Each vial will be labeled as required per country requirement. The ancillaries such as injection needles (BD precision glide needle 30G x ½ inch), hypodermic needle (18 G 1 x ½ inch), BD blunt filter needle (5 micron with blunt fill tip reference), and BD hypodermic 3-part Luer Lok syringes (1 ml) will be supplied to the study centers.	140
Eylea	(Dimeric Glycosylated recombinant fusion glycoprotein)	40 mg/ml Dosage Formulation: 2 mg (0.05 mL) – Unit Dose Strength(s)	Eylea will be provided as single dose prefilled syringes. Each prefilled syringe will be labeled as required per country requirement. Injection needles (BD Precision glide needle 30 G x ½ inch will be supplied to the study centers.	140

IMP Calculation: Treatment Plan:

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

Manufacturer's name and address as per COA and GMP:

a. **AVT06:**
Patheon Italia S.p.A. (part of Thermo Fisher Scientific), Viale G.B. Stucchi 110, 20900 Monza (MB), Italy

b. **Eylea:**
Bayer AG, Müllerstraße, 178, 13353 Berlin, Germany.

c. **Batch and Expiry:**

Active: Batch# E230597-00 1,2L; 06 / 2023
Comparator/Placebo: Batch# E230597-OO12L; Expiry: 06/2023

d. **Packaging site and address:**
Almac Clinical Services (ACS), 20 Seagoe Industrial Estate, Craigavon T863 5QD, Northern Ireland.

vi. Number of subjects to be recruited: 28 Subjects

vii. Anticipated cost of the project: USD 249,556/-

viii. Study design & details:

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	444 participants globally 28 participants from Pakistan
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)
Primary Purpose	Treatment
Official 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)
Estimated Study Start Date :	28th June, 2022
Estimated Primary Completion Date :	February, 2023
Estimated Study Completion Date :	December, 2023

ix. Arms & Intervention:

ARM	INTERVENTION/TREATMENT
Experimental: AVT06 (proposed aflibercept biosimilar) Patients will receive 1 IVT injection of AVT06 every 4 weeks for the first 3 consecutive doses, followed by 1 IVT injection every 8 weeks through study completion.	Drug: AVT06 (proposed aflibercept biosimilar) Patients will receive IVT injections of AVT06
Experimental: Eylea® (Aflibercept) Patients will receive 1 IVT injection of Eylea® every 4 weeks for the first 3 consecutive doses, followed by 1 IVT injection every 8 weeks through study completion.	Drug: Eylea® (Aflibercept) Patients will receive IVT injections of Eylea®

x. Eligibility Criteria

Inclusion Criteria:

a. Subject must be ≥50 years of age, at the time of signing the informed consent.
b. Subjects must be diagnosed with neovascular (wet) AMD in the study eye.
c. Subjects must have active, treatment naïve, subfoveal CNV lesions secondary to neovascular (wet) AMD.
d. Willingness and ability to undertake all scheduled visits and assessments.

Exclusion Criteria:

e. Any prior systemic treatment with anti-VEGF therapy
f. Any condition that, in the Investigator´s opinion, can interfere with full participation in the study, including administration of the study treatment and attending required visits; can pose a significant risk to the participant, or interfere with interpretation of study data
g. Prior treatment with any investigational drugs within 30 days or 5 half-lives (whichever is longer) of the previous investigational treatment before initiation of the study treatment or concomitant enrollment in any other clinical study involving an investigational study treatment
h. Subjects not suitable for participation, whatever the reason, as judged by the Investigator, including medical or psychiatric conditions, or participants potentially at risk of noncompliance to study procedures.

xi. Proposed Clinical Trial Sites & PI/Co-PI details:

Proposed CTS	Site PI/Co-PI
The Aga Khan University Hospital, Karachi.	Dr. M.A. Rehman Siddiqui (National PI)
Shifa International Hospital, Islamabad	Dr. Amer Awan (Site PI)
Avicenna Medical College and Hospital, Lahore.	Dr. Khalid Mahmood (Site PI)
Central Park Teaching Hospital, Lahore	Dr. Usman Imtiayz (Site PI)
Al-Shifa Trust Eye Hospital, Lahore	Dr. Ume Sughra (Site PI)
Maroof International Hospital, Islamabad	Dr. Jahanzeb Durrani (Site PI)

3. The study carried out under the supervision of Dr. M.A. Rehman Siddiqui (National PI). The trial comprises of following primary objective(s);

a. Change from baseline to Week 8 in Best-corrected Visual Acuity (BCVA) [Time Frame: Week 8]

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. 566016616739, dated 11th October, 2022
3	Investigator Brochure (s)	IB (AVT06)Version 3.0, dated 19th May, 2022 is attached
4	Final protocol	Attached Protocol No. AVT06-GL-C01 Version 2.0, dated 21st December, 2021. * Insurance invoice for Pakistan is attached (Page 514/Corr.)
5	Informed consent and participant information sheet (Urdu to English)	Attached.
6	List of participating countries	Argentina, Brazil, Bulgaria, Czech Republic, Georgia, Hungary, India, Japan, Latvia, Poland, Russia, Ukraine, Slovakia, Pakistan and South Africa.
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.	Attached Already mentioned above. * Further a list of ancillary items to be imported & used in the trial is attached (697-700/Corr.) List is also reproduced under. Justification is required.(Annex-I)
9	Site of the trial	i. The Aga Khan University Hospital, Karachi. ii. Shifa International Hospital, Islamabad. iii. Avicenna Medical College and Hospital, Lahore. iv. Central Park Teaching Hospital, Lahore. v. Al-Shifa Trust Eye Hospital, Lahore. vi. Maroof International Hospital, Islamabad.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB/ERC approval along with composition are attached: i. The Aga Khan University Hospital, Karachi. (Page 326-328/Corr.) ii. Shifa International Hospital, Islamabad. iii. Avicenna Medical College and Hospital, Lahore. (Page 335-337/Corr.) iv. Central Park Teaching Hospital, Lahore. (Page 321-325/Corr.) v. Al-Shifa Trust Eye Hospital, Rawalpindi (Page 310-320/Corr.) vi. Maroof International Hospital, Islamabad. (Page 331-334/Corr.)
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter no.4-87/NBC-855/22/456, dated 07th October, 2022 (for a period of **Six** months).
12	CV's of the Investigators	CVs of following experts are attached. **xviii.** Dr. M.A. Rehman Siddiqui (National PI), AKUH, Karachi. (Page263-268/Corr.) **xix.** Dr. Amer Awan (Site PI), Shifa International Hospital, Islamabad. (Page 278-294/Corr.) **xx.** Dr. Khalid Mahmood (Site PI), Avicenna Medical College and Hospital, Lahore. (Page 270-271/Corr.) **xxi.** Dr. Usman Imtiayz (Site PI), Central Park Teaching Hospital, Lahore. (Page 272-277/Corr.) **xxii.** Dr. Ume Sughra (Site PI), Al-Shifa Trust Eye Hospital, Lahore. (Page 295-309/Corr.) **xxiii.** Dr. Jahanzeb Durrani (Site PI), Maroof International Hospital, Islamabad. (Page269/Corr.)

13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following are attached: i. Alvotech hf, Sæmundargata 15-19, Reykjavik, 101, Iceland. ii. Alvotech hf, Lambhogavegur 7, Reykjavik, 113, Iceland. iii. Patheon Italia S.P.A., Viale G.B. Stucch|, 110 - 20900 MONZA (MB) (For manufacture of IMPs i.e.) iv. * Clarification regarding MAH, Manufacturer & Importer of the IMP need to be provided. Further link between following: • Alvotech hf, Sæmundargata 15-19, Reykjavik, 101, Iceland. • Alvotech hf, Lambhogavegur 7, Reykjavik, 113, Iceland. • Patheon Italia S.P.A., Viale G.B. Stucch|, 110 - 20900 MONZA (MB) • Charles River Laboratory. ** CoPP for Eylea® 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.	444 participants globally 28 participants from Pakistan.
19	Name of Monitors & Clinical Research Associate	M/s IQVIA Solutions Pakistan (Pvt) Ltd., Karachi, Pakistan. i. Bharti Kachela- Karachi. ii. Asjid Ali Arshad-Islamabad. iii. Mahir Ahmed & Muhammad Asif Mahmood-Lahore
20	Evidence of registration in country of origin.	Registration letter of Eylea® manufactured by M/s Bayer AG, Berlin, Germany is not provided.
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	21 Months.
23	Undertaking on Stamp paper	Attached.

05. Following additional documents are also attached:

i. Investigational Medicinal Product (IMP) Dossier (Page 779-1094/Corr.)
ii. ALVOEYE Patient Brochure/Information Pamphlet. (1097-1101/Corr.)
iii. Patient ID Card (1102-1106/Corr.)
iv. Visit Reminder Card (1107-1111/Corr.)
v. ALVOEYE Site Poster (1112-1114/Corr.)

06. After initial scrutiny following shortcomings are recorded:

ix. Clarification regarding MAH, Manufacturer & Importer of the IMP need to be provided. Further link between following:

- Alvotech hf, Sæmundargata 15-19, Reykjavik, 101, Iceland.
- Alvotech hf, Lambhogavegur 7, Reykjavik, 113, Iceland.
- Patheon Italia S.P.A., Viale G.B. Stucch|, 110 - 20900 MONZA (MB)
- Charles River Laboratory.

x. CoPP/Free Sale Certificate for Eylea® is not provided.
xi. Registration letter of Eylea® manufactured by M/s Bayer AG, Berlin, Germany is not provided.
xii. A list of ancillary items to be imported & used in the trial is attached. As a number of Medical Devices are mentioned the list, so, clarification regarding their registration/enlistment status is required or NOC from MD&MC Division of DRAP is required for import.

07. Shortcomings communicated to Principal Investigator & nominated CRO for fulfillments on 08th November, 2022, response is awaited. Reply from Dr. M.A. Rehman Siddiqui, The Aga Khan University Hospital, Karachi, Pakistan, Stadium Road, Karachi, received on 16th November, 2022.

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

Sr.	Descriptions / Shortcomings	Reply	Remarks
01	Clarification regarding MAH, Manufacturer & Importer of the IMP need to be provided. Further link between following: i. Alvotech hf, Sæmundargata 15-19, Reykjavik, 101, Iceland. ii. Alvotech hf, Lambhogavegur 7, Reykjavik, 113, Iceland. iii. Patheon Italia S.P.A., Viale G.B. Stucch|, 110 - 20900 MONZA (MB) iv. Charles River Laboratory.	**i. For Eylea:** Charles River Biopharmaceutical, Services GmbH, Max-Planck-Str. 15 A 40699 Erkrath, Deutschland. Annexure No. 1.1 GMP Certificate **(Page 1234-1240/Corr.)** **ii. For the Alvotech Biosimilar:** Almac Clinical Services (ACS), Seagoe Industrial Estate, 9 Charlestown Road, Craigavon, Northern Ireland, 8T63 5PW, UNITED KINGDOM. Annexure No. 1.2 GMP Certificate **(Page 1246-1250/Corr.)** ***** **(**I hereby certify that the batch of **Labelled carton containing 1x Eylea 40mg/ml (0.9ml fill) pre-filled syringe or AVT06 40mg/ml (0.278ml fill) vial** listed below has been subject to review confirming compliance with the relevant requirements.) **iii.** GMP Certificate of M/s Bayer AG, Berlin Germany is attached. (Page 1354-1357/Corr.)	---
02	CoPP/Free Sale Certificate for Eylea® is not provided.	i. Certificate of Pedigree and Product handling (Free Sale) is attached Annexure No. 2.1 (Page 1246/Corr.) ii. The SmPC summary with product registration, marketing authorization & Composition details. Annexure No. 2.2 (Page 1252-1253/Corr.) iii. Eylea is stablished brand (EUl1ll2l797l00l) that's why Sponsor provided the detailed Product information attached: SUMMARY OF PRODUCT CHARACTERISTICS Annexure No. 2.3. (Page 1254 /Corr.)	---
03	Registration letter of Eylea® manufactured by M/s Bayer AG, Berlin, Germany is not provided.	SmPC instead of registration letter of Eylea® manufactured by M/s Bayer AG, Berlin, Germany is attached as product already registered. Online verification document is attached. (Page 364/Corr.)	---
04	A list of ancillary items to be imported & used in the trial is attached. As a number of Medical Devices are mentioned the list, so, clarification regarding their registration/enlistment status is required or NOC from MD&MC Division of DRAP is required for import.	All the supplies, ancillary and equipment is sponsor's property and will return after the study. Sponsor will make all shipments DDP and deposit security deposits until the return of shipments as per Pakistan Customs rules. The same is covered in main executed clinical Trial Agreements with the sites under the clause No. J. The updated list is attached in Annexure No. 3.1. (Page 1349-1351/Corr.)	---

09. Secretary CSC presented the case before the CSC, Dr. M. A. Rehman Siddiqui, PI of the trial also joined the meeting through Zoom & responded to the queries raised by the CSC members. The Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to approve the Phase-III 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)", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Sites:

i. The Aga Khan University Hospital, Karachi.
ii. Shifa International Hospital, Islamabad.
iii. Avicenna Medical College and Hospital, Lahore.
iv. Central Park Teaching Hospital, Lahore.
v. Al-Shifa Trust Eye Hospital, Lahore.
vi. Maroof International Hospital, Islamabad.

A total of 28 subjects will be enrolled in the study and trial duration will be 21 Months. Following quantities of IMPs along with ancillary items attached as Annex-I will be imported for the trial:

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 %willbe25Yo:
Active: 112 x 25% = 28; Total Import Quantity: 112 + 28 = 140
Comparator: 112 x 25% = 28; Total Import Quantity: 112 + 28 = 140

AGENDA ITEM XII:

APPLICATION FOR REGISTRATION AND APPROVAL OF A PALCEBO–CONTROLLED, RANDOMIZED, CLINICAL TRIAL TITLED "ROLE OF PEGLYATED INTERFERON IN SARS-COV2 VIRAL CLEARANCE AND IMMUNOLOGIC OUTCOMES IN COVID-19 PATIENT USING BLOOD TRANSCRIPTION PROFILING", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-15/2022-DD (PS)

Application is from Dr. Zahra Hassan, **Ph.D. Microbiology** (42201-8527073-8), Professor & Consultant, Molecular Pathology, Department of Pathology & Laboratory Medicines, Aga Khan University Hospital, Stadium Road, Karachi, dated 22nd August, 2022. Wherein request has been made for approval of subject **Phase-II** Clinical Trial, which will be carried out at Clinical Trial Unit, Aga Khan University Hospital, Karachi. Application is on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide challan no. 983684863, dated 18th August, 2022.

2. 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.:
Peg-INF Injection Registration No.063211

ii. **Sponsor:** Details not provided.

iii. **Purpose of trial:** The purpose of this study is to evaluate, easily accessible, cost-effective treatment for COVID-19 is required especially in a low resource setting such as Pakistan. Through our previous studies, we have shown that, individuals who show, limited signs and symptoms of COVID-19 have a stronger immune response called the "Type-I Interferon response". Interferon can also be given as an injection and is commonly used to treat hepatitis viral infection. We propose to test the administration of PEG interferon in patients with COVID-19, a drug, and investigate its effect on the immune response and the ability of the body to clear the virus. To investigate the ability of peg IFN in symptomatic cases with minimal disease:

- **a.** in early clearance of SARS-CoV2 virus
- **b.** favorable RNA transcriptional profiling as evidenced by interferon-stimulated genes
- **c.** Improvement in serum biomarkers.

iv. Subject selection criteria:

a. Inclusion Criteria

Participants will be of either gender between 30 and 60 years of age with a positive qPCR for SARS CoY-2 and symptoms for 7 days or less. Only patients with minimal disease (WHO ordinal scale 1-3) will be included (11).

b. Exclusion Criteria

Individuals with a prior history of COVID-19 immunocompromised individuals such as those with, CKD, RA, malignancy, known chronic viral infections such as hepatitis viruses, HIV, or, on corticosteroid treatment in the past four weeks. Patients with autoimmune disease, carcinoma, chronic kidney disease, known viral disease (like Hepatitis-B, C or HIV), Tuberculosis, pregnant or lactating women. Patients enrolled in any other COVID-19 therapeutic trial.

c. Subjects recruitment & follow up processes:

Patients will be identified using the ongoing Infectious Diseases and Internal Medicine telemedicine clinic at the Aga Khan University. Once identified consent will be obtained over the telephone by the study team. After consent randomization of the intervention will be done through the CTU, AKU, to either the peg IFN (180mg sub cutaneous) or placebo (saline) to the study team.

Subject Follow up

Subjects will be administered the study drug (peg IFN vs saline) at home using trained study personal. All subjects will be observed for 30 minutes' post-administration for any adverse effects Following enrollment and study drug administration, patients will be followed daily over the phone for 14 days for solicitated and un-solicitated side effects as well as to assess the clinical symptoms. One formal teleclinic appointment will also be booked with an infectious diseases physician between day 5 and 7 of enrollment. However, if any clinical worsening is felt by the study team on daily follow-ups, an earlier appointment (within 24 to 48 hours) will be arranged.

Sampling Strategy:

Patients will be identified using the ongoing Infectious Diseases and Internal Medicine telemedicine clinic at the Aga Khan University. Once identified consent will be obtained over the telephone by the study team. After consent randomization of the intervention will be done through the CTU, AKU, to either the peg IFN (180mg sub cutaneous) or placebo (saline) to the study team.

Expected outcomes:

We expect to follow increased recovery of COVID-19 patients through improvements in LDH, ferritin and NLR to be associated with rapid clearance of SARS-CoV-2 accompanied by up regulation of ISGs in the treatment group who are given interferon therapy.

v. Number of subjects to be recruited: 24 Subjects

vi. Anticipated cost of the project: PKR 2,820,900/-

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 challan no. 983684863, dated 18th August, 2022.
3	Investigator Brochure (s)	As PEG-Interferon is a registered product, its PIL is attached in place of IB.
4	Final protocol	Attached but is not according to ICH-GCP Guidelines. Insurance details are not provided in protocol.

		**. Protocol is not signed by Sponsor & PI.
5	Informed consent and participant information sheet (Urdu to English)	Verbal/telephonic Consent Form are attached instead of Informed Consent Forms. It is informed that, ICFs as per ICH-GCP Guidelines need to be provided. * Compensation/Insurance details are not provided.
6	List of participating countries	Pakistan only.
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.	24 Subjects 12 Active 12 Placebo. Details regarding placebo & its manufacturing & blinding of IMPs is not provided.
9	Site of the trial	Clinical Trial Unit, Aga Khan University Hospital, Karachi.
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 07th April, 2022 along with amendment approval letter dated 17th May, 2022 is attached. (Previously Dr. Faisal Mahmood was PI of the trial)
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter No.4-87/COVID-109/22/51, dated 21st July, 2022 (for a period of **Six** months).
12	CV's of the Investigators	CVs of PI, Zahra Hasan Ph.D. (Medical Microbiology) (65-67/Corr.)
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate of M/s BF Biosciences Ltd., 05-KM, Sundar, Raiwind Road, Lahore & CoPP for Peg-INF Injection (Peginterferon alpha-2a….180µg) mfd: by M/s BF Biosciences Ltd., Lahore is attached.
14	Pre-clinical/clinical safety studies	Not provided as IMP is a registered product. PIL is attached.
15	Summary of Protocol	Attached but not as per ICH-GCP Guidelines.
16	Summary of Investigator Brochure	As IMP is a registered product. PIL is attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Total 24 COVID-19 positive Subjects.
19	Name of Monitors & Clinical Research Associate	---
20	Evidence of registration in country of origin.	---
21	Copy of registration letter (if registered in Pakistan)	Attached.
22	Sample of label of the investigational product / drug.	Attached label is a commercial one & not as per ICH-GCP Guidelines.
22	Duration of trial	Approximately 12 Months.
23	Undertaking on Stamp paper	Not provided.

04. After initial scrutiny following shortcomings are recorded:

i. Attached protocol is not according to ICH-GCP Guidelines.
ii. Insurance details are not provided in protocol.
iii. Protocol is not signed by Sponsor & PI.
iv. Recruitment of subject with any medical check-up & telephonic consent without any is not as per ICH-GCP Guidelines. It is informed that, ICFs as per ICH-GCP Guidelines need to be provided.
v. Compensation/Insurance details are not provided in protocol & in the ICF.
i. Attached label is a commercial one & not as per ICH-GCP Guidelines.

ii. As per study protocol, IMPs will be administered at home & blood samples also will be withdrawn at home. Clarification required that, how a phase-II clinical trial subjects may be treated at home & in case of emergency what can be done at home as for a Phase-I/II clinical trial tertiary care facilities should be available for treatment of patients.
iii. AKUH Clinical Laboratory is not approved as a Bio-Analytical Laboratory from DRAP to act as Laboratory for Clinical Trials. Further, Clarification required for PK/PD Studies if required in the subject Clinical Trials.
iv. Procedure for blinding of Active & Placebo is not provided.
v. Details regarding placebo, its manufacturing & blinding of IMPs is not provided.
vi. Attached label is a commercial one & not as per ICH-GCP Guidelines.
vii. Trial sponsor details are not provided.

05. Accordingly, shortcomings communicated to Principal Investigator & nominated CRO for fulfillments on 03rd November, 2022, response is still awaited.

06. The Secretary presented the case before CSC & 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. Attached protocol is not according to ICH-GCP Guidelines.
ii. Insurance details are not provided in protocol.
iii. Protocol is not signed by Sponsor & PI.
iv. Recruitment of subject with any medical check-up & telephonic consent without any is not as per ICH-GCP Guidelines. It is informed that, ICFs as per ICH-GCP Guidelines need to be provided.
v. Compensation/Insurance details are not provided in protocol & in the ICF.
vi. Attached label is a commercial one & not as per ICH-GCP Guidelines.
vii. As per study protocol, IMPs will be administered at home & blood samples also will be withdrawn at home. Clarification required that, how a phase-II clinical trial subjects may be treated at home & in case of emergency what can be done at home as for a Phase-I/II clinical trial tertiary care facilities should be available for treatment of patients.
viii. AKUH Clinical Laboratory is not approved as a Bio-Analytical Laboratory from DRAP to act as Laboratory for Clinical Trials. Further, Clarification required for PK/PD Studies if required in the subject Clinical Trials.
ix. Procedure for blinding of Active & Placebo is not provided.
x. Details regarding placebo, its manufacturing & blinding of IMPs is not provided.
xi. Attached label is a commercial one & not as per ICH-GCP Guidelines.
xii. Trial sponsor details are not provided.
xiii. 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.

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

AGENDA ITEM XIII:

DRUGS EVALUATION & DESTRUCTION INSPECTION REPORT & APPLICATION FOR EXTENSION IN TRIAL DURATION OF CLINICAL TRIAL TITLED "A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE-II CLINICAL TRIAL TO EVALUATE THE EFFICACY & SAFETY OF CBP-307 IN SUBJECTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS (UC)" F.NO.03-59/2021 DD (PS).

Report is submitted by Mr. Ahmad Din Ansari (Inspection Panel Coordinator), the then Additional Director, Pharmacy Services Division-DRAP, dated 07th July, 2022. Inspection report regarding destruction of expired/unused Investigational Medicinal Product (IMPs) of subject Clinical

Trial, in reference to this Division's letter bearing even number dated 01st February, 2022. Discussion/Conclusion of inspection is as follows:

Discussion/Conclusion:

i. *The above observations and deficiencies in documents were discussed with the Director CTU/PI of the trial under reference and other technical staff working in CTU' It was undertaken to correct all the pointed-out deficiencies and further improve the documentation as per the standard practice.*
ii. *The PI and his team agreed with the panel to the fact that the IMP should be destroyed/disposed off as per the procedure to be finalized by the CTU/Trial Site in the light of the SOP provided by of CRO in consultation with the sponsor of the study or manufacturer of IMP.*
iii. *The PI was also advised that the CRO should be informed about the proceedings of the inspection and be asked to conduct audit of trial at some predefined intervals to address the shortcomings/deficiencies if any pointed out by them during the trial proceedings.*
iv. *The destruction/disposal of the expired/unutilized stocks of IP was not undertaken due to the reason that the study/trial was still underway and the SOP for destruction/safe disposal was yet to be acquired by the PI from sponsor of the study/manufacturer of IP and CRO of the study.*

2. Further an application from Dr. Saeed Hamid (PI), Director, Clinical Trial Unit, Professor & Consultant Gastroenterologist, Aga Khan University Hospital, Karachi, submitted on 18th July, 2022. Wherein application is a reminder- application for Extension in duration of study "A multicenter. randomized, double-blind, placebo-controlled phase-II clinical trial to evaluate the efficacy and safety of CBP-307 in subjects with moderate to severe ulcerative colitis (UC)".

3.. Brief summary regarding trial is as follows:

i. Trial approval date : 17th March 2021.
ii. Trial duration : 13th Months.
iii. Trial duration expired on : 16th March 2022.
iv. Number of subjects approved : 07 Subjects.
v. Subjects recruited in the study: 06 Subjects.
vi. Approved IMPs quantity:

S.No.	Investigational Drugs	Brand Names	Manufacturer	Quantity
01	CBP-307 Capsules.	Generic	M/s China Gateway Pharmaceutical Development Co. Ltd., China. **Sponsored by :** Suzhou Connect Biopharmaceuticals, Ltd., China.	Total 203 cartons (5771 bottles) required for the trial.

vii. IMPs Imported till date : 5771 bottles (Imported all approved quantity).

4. Applicant/PI attached following documents with application:

i. Copy of registration letter number CT-0024 of subject trial.
ii. Copy of import licence for IMPs.
iii. Copy of six-monthly progress report along with protocol deviation report.

Principal Investigator Name/Site No.	Total Number of Subjects Screened	Total Number of Subjects Screen failed	Total Number of Subjects withdrew consent	Total Number of patients randomized	Serious Adverse Events (Aug-2021 to Dec-2021)
Dr. Saeed Hamid /2151	11	04	01	06	No serious adverse event was reported.

iv. AKUH-IRB approval letter, dated **03rd December 2021** for extension in trial duration for **one year**.
v. NBC approval letter reference number 4-87/NBC-591/21/965, dated **24th December 2021**, for extension in trial duration for **one year**.
vi. Prescribed processing fee (i.e. Rs.25000-/), paid vide challan No. 91142037653, dated 16th March, 2022.

5. Inspection report & application for extension in the trial duration as approved by IRB & NBC is placed for consideration of CSC, please.

6. The Secretary presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to approve extension in the trial duration as approved by the IRB & NBC, for a period of one year w.e.f. ***24th December 2021****.*

Further, the Committee delegated the power to the Chairman CSC for constitution of the inspection panel to visit the site for verification/confirmation & destruction of un-used/expired IMPs as per SOPs. Nominated panel after inspection will generate a report as per guidelines and will be placed again before the CSC for consideration.

AGENDA ITEM XIV:

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. *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. i. For trial use 100 Tablets ii. Retention Samples 500 Tablets iii. Total 600 Tablets. * 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 composition of committee i.e. names and designation of members.	Attached.
11	Approval of National Bio-ethics Committee (NBC)	Attached. 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: i. Principal investigator: Professor Dr. M. Raza Shah T.I. (Ph.D., Post Doc) ii. Co-Principal investigator: Dr. Izhar Hasan (MD, Ph.D.) iii. Clinical investigator: Dr. Syed Ali Talha Raza (MBBS) iv. Technical Coordinator: Dr. Naghma Hashmi (Ph.D.) v. Study Coordinator: Dr. Shafiullah (Ph.D., CCRP)

13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not provided. 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. 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. 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:

i. 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.
ii. Justification required for quantity mentioned in reference to quantity to be utilized in trial.
iii. 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.
iv. PI need to provide details regarding brand of IMP utilized in the trial which is manufactured by M/s Pharms Ops, Inc., NJ, USA.
v. 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.
vi. 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:

Sr.	Descriptions / Shortcomings	Reply	Remarks
01	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	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	It was informed & advised to revise/amend study protocol & incorporate required details & submit revised protocol along with IRB & NBC approvals. But

<table>
<tr><td></td><td>revise/amend study protocol & incorporate required details & submit revised protocol along with IRB & NBC approvals.</td><td>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>

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>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:
<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 conditions, and (3) retained for a specified period.
Thus, approximately 500 Tablets will be archived in the trial center for a period of 5 years.</td><td>---</td></tr>
<tr><td>03</td><td>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.</td><td>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</td><td>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.</td></tr>
<tr><td></td><td>Attached GMP certificate is from the manufacturer itself GMP from Regulatory Authority of the Country of</td><td>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</td><td>It is informed again that, GMP Certificate for M/s Pharms Ops, Inc., NJ, USA issued by the Drugs</td></tr>
</table>

	Origin (i.e. US-FDA) is required.	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). 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).	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.
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: i. Anaflex ii. Salflex iii. Disalcid iv. 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
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. Accordingly, after approval shortcoming communicated to applicant on 14th November, 2022.

09. Moreover, it is submitted that, as applied study is a Phase-I Clinical Trial & it is suggested that, a trial specific inspection may be carried out to verify the available facilities at the proposed site & its status (primary, secondary & tertiary care facility) & its feasibility for the subject trial.

10. Secretary CSC presented the case before the Committee & 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.

AGENDA ITEM XV:

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 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 12th August, 2022. Wherein request has been made for approval of subject Clinical Trial on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide challan no. 3306333872, dated 26th July, 2022.

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

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

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

iii. **Arms & Interventions:**

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

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

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

Dosage Form: Aerosol.
Composition: Recombinant Cytokine Gene Derived Protein.
Route: Inhalation.

B. Placebo: Saline

Dosage Form: Aerosol
Route: Inhalation.

C. Quantity required:

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

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

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

vii. Study design & details:

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

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

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

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

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs. 200,000/- deposited vide challan no. 3306333872, dated 26th July, 2022 * Original fee challan (DRAP's Copy) need to be provided.
3	Investigator Brochure (s)	IB Version 2.0 dated 17th December is attached
4	Final protocol	Attached Protocol No. CRO-009-NOV-(JH509)-2022/Protocol/1.1 Version 1.1, dated 09th November, 2022 * Insurance policy details / procedure for trial related health injury compensation is need to be clarified & should be incorporated in trial protocol.

5	Informed consent and participant information sheet (Urdu to English)	Attached but following points need to be clarified * Details regarding Insurance firm/MoU need to be provided
6	List of participating countries	Hong Kong, China & Pakistan. * Details regarding other participating countries is not provided.
7	Phase of trial.	Phase – III
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	The required quantity of IMPs is as follows: iii. Novaferon® (7104 Vials) iv. Placebo (7104 Vials)
9	Site of the trial	i. Dow University Hospital, Karachi. ii. The Indus Hospital & Health Network, Karachi. iii. Creek General Hospital, Karachi.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Ref: # ICCBS/CBSCR/IEC/LET-048/2022 dated 07th March, 2022.
11	Approval of National Bio-ethics Committee (NBC)	Reference No.4-87/COVID-105/22/06, dated 07th July, 2022 (for a period of **Six** months).
12	CV's of the Investigators	CVs of following experts are attached. **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: • Copy of GMP Certificate M/s Genova Biotech (Qingdao) Co., Ltd, No. 19, Keyuanwei 3rd Road, Laoshan District, Qingdao, Shandong Province, China. • Copy of CoPP for Novaferon® (Recombinant cytokine gene derived protein injection) 10µg/1.0ml/vial, is attached. * GMP Certificate for M/s Emballages Spectrum Packaging Inc., 617 rue McCaffrey, Saint-Laurent, QC H4T 1N3, Canada & CoPP or other evident document issued by relevant regulatory body for placebo is not provided.
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Summary of Ibis not provided.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	111 Subjects * Details regarding subjects distribution among other countries involved in trial need to be provided.
19	Name of Monitors & Clinical Research Associate	Dr. Muhammad Imran, M/s Global Scientific R&D, Karachi (CRO) * There are two different CRO(s) involved in trial, which needs to be clarified that which CRO has been notified/engaged
20	Evidence of registration in country of origin.	Copy of CoPP for Novaferon® (Recombinant cytokine gene derived protein injection) 10µg/1.0ml/vial, is attached. Copy of translation & New Drug Certificate issued by China Food & Drug Administration. Copy of COA also attached
21	Copy of registration letter (if registered in Pakistan)	Not applicable.

22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	The treatment period with investigational drug during the trial is 07 days & follow up will be up to 28 days. The trial is expected to completed in **six (06)** months.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings were recorded:

xiii. Original challan (DRAP's copy) need to be provided.
xiv. Summary of Investigator's Brochure is not provided.
xv. Insurance policy details / procedure for trial related health injury compensation is need to be clarified & should be incorporated in trial protocol.
xvi. 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.
xvii. Details regarding subject's distribution among other countries involved in trial need to be provided.
xviii. 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.
xix. 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, Page 344/Corr.)	---
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, Page 345-355/Corr.).	---

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, Page 356-361/Corr.)	---
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 Page 362-363/Corr.)	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 each country. Phase III trial on the same formulation i.e. Inhaled Novaferon (NOVATION-I) in Hospitalized Patients with Moderate to Severe COVID-19 patients has been approved in different countries including Turkey, Argentina Brazil, Colombia, South Africa and Chile.	Previously it was informed in the application that, the trial will be carried out in Hong Kong, China & Pakistan. Further, as claimed that, it is a different trial from NOVATION, another trial enlisted on U.S. Trial Registry with identifier number NCT05172037 & its Sponsor is M/s Genova Inc., instead of M/s Genova Biotech (Qingdao) Co. Ltd., China & as per updated record its completion date was June, 2022 & its only site was Tokyo Shinagawa Hospital, Tokyo, Japan. Clarification in this regard need to provided & link between M/s Genova Inc., Japan & M/s Genova Biotech (Qingdao) Co. Ltd., China need to be explained.
VI	There are following two different CRO(s) involved in trial, which needs to be clarified that which CRO has been	Please find the Authorization letter from the sponsor attached	Authorization from study sponsor M/s Genova Inc., Japan need to be provided.

	notified/engaged by sponsor & evident document (agreement/letter) need to be provided. **M/s CBSCR-ICCBS, University of Karachi** **M/s Global Scientific R&D, Karachi (CRO)**	with this response letter (See Appendix-5, Page 365/Corr.).	
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.*	a. Yes, it is the same trial and was registered in us Trial Registry b. Genova Biotech (Qingdao) co., Ltd is the wholly owned subsidiary of Genova Inc., and responsible for manufacturing Novaferon (IP) for the clinical trials sponsored by Genova Inc. In this regard, Genova Biotech (Qingdao) Co., Ltd should be considered as Sponsor as well. c. Genova Biotech (Qingdao) co., Ltd is the wholly owned subsidiary of Genova Inc. d. Yes, Novaferon is registered in the names of Genova Biotech (Qingdao) co" Ltd. And M/s Genova Inc. As these two companies are in the same group.	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.

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. Moreover, it is requested that, as applied site is not a health care facility (Primary, Secondary or Tertiary), so, it is suggested that, a trial specific inspection may be carried out to verify available facilities at the proposed site & its status as a "Primary, Secondary or Tertiary Care Facility & its feasibility for the subject trial.

12. Secretary CSC presented the case the case before & 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.

AGENDA ITEM XVI:

REQUEST FOR APPROVAL OF PHASE-I CLINICAL TRIAL TITLED "RANDOMIZED, DOUBLE BLINDED, PARALLEL PLACEBO CONTROLLED CLINICAL TRIAL", TO EVALUATE THE SAFETY OF DIETRY HERBAL HEALTH SUPPLEMENT-I (DHA-I), DEVELOPED FOR THE TREATMENT AND/OR MANAGEMENT OF PARKINSON'S DISEASE". F. No.03-63/2021-DD (PS).

Application was submitted by Prof. Dr. Muhammad Iqbal Choudhry (CNIC-42101-1124466-5), Director ICCBS-University of Karachi, Karachi, dated 26th March 2021. Wherein the request has been made for registration of the subject clinical trial. Application is on prescribed form-II along with a prescribed fee of Rs.200000/- paid vide challan number 2062152, dated 24th March 2021.

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

i. **Sponsor:** M/s Dr. Punjwani Center for Molecular Medicine & Drug Research, Karachi.

ii. **Name of Investigational products**:
   a. Dietary Health Supplement-I

iii. Primary Objective of the study:
   a. To investigate the safety of the ***D***ietary ***H***erbal Health ***S***upplement-I **(DHS-I)** in healthy people (aged 40years old & above)

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	Rs.200000/- deposited vide challan no. 2062152, dated 24th March 2021.
3	Investigator Brochure (s)	Attached. Edition 1.0, dated March 24,2021.
4	Final protocol	Attached. Version 1.0
5	Informed consent and participant information sheet (Urdu to English)	Informed consent form in English, Urdu & Sindhi language is 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.	A total of 50 healthy participants aged 40 years old and above will be enrolled in the study. Eligible participants will be divided into three groups, group 1 will receive 6 g of DHS - 1, group 2 will be received 12 g of DHS - 1 thrice a day after each meal and group 3 will be given placebo as control group for 3

		months. According to this dosage the total quantity of the drug used for trial will be approximately 10 kg. Multiple use glass jars, containing 500 g supplement / jar will be given to each patient per month.
9	Site of the trial	Center for Bioequivalence Studies and Clinical Research (CBSCR), International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, Karachi. CTS-0046.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB approval from Center for Bioequivalence Studies and Clinical Research (CBSCR), International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, Karachi, is not provided.
11	Approval of National Bio-ethics Committee (NBC)	Attached. 1. Ref:No.4-87/NBC-579/20/1261, dated 08th February 2021.
12	CV's of the Investigators	CVs of following (PIs) are attached: vi. Prof. Dr. Iqbal Choudhry, Director ICCBS-University of Karachi, Karachi.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	No details of manufacturer of the IMPs is attached. GMP certificate 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 but not as per CIOMS format.
18	No of patients to be enrolled in each center.	50 Subjects.
19	Name of Monitors & Clinical Research Associate	Dr. M. Hassan Auj, University of Karachi, Karachi.
20	Evidence of registration in country of origin.	Not applicable as the product is for Phase-I trial & not registered yet.
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	03-06 Months.
23	Undertaking on Stamp paper	Not provided.

04. After initial scrutiny following shortcomings observed:

i. IRB approval from Center for Bioequivalence Studies and Clinical Research (CBSCR), International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, Karachi, is not provided.
ii. No details regarding manufacturer of the Investigational Medicinal Product (IMPs) is attached.
iii. Licence to manufacture for experimental purpose is required under chapter-II, Rule 3(v) & 21 of Schedule-G of LRA Rules 1976 is required for manufacture of IMPs.
iv. GMP certificate of the IMPs manufacturer is not provided.
v. Provided adverse event reporting form is not as per CIOMS format.
vi. Undertaking on Stamp paper

05. In the view of above, it is proposed that the above-mentioned shortcomings may communicate to the applicant, DFA attached.

06. Further, it is submitted that technical documents (i.e. Pre-Clinical Studies, Toxicological Studies, Study Protocol & investigator's brochure etc.) may be forwarded to experts for review & evaluation under sub-rule 4 of rule 7 of the Bio-Study Rules 2017, please.

07. Accordingly, shortcoming letter was communicated to applicant on 13th April, 2021 & reminder issued on 05th May, 2021.

08. Reply from Prof. M. Iqbal Choudhry, Director ICCBS-University of Karachi, Karachi, received on 17th May, 2021. Applicant response for shortcomings is as follows:

S.No.	Shortcomings	Reply
01	IRB approval from Center for Bioequivalence Studies and Clinical Research (CBSCR), International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, Karachi, is not provided.	IRB/IEC approval letter dated 17th May 2021 is attached. (Page 336/corr.)
02	No details regarding manufacturer of the Investigational Medicinal Product (IMPs) is attached.	License of the Searle Company limited is attached. (Page 338/corr.)
03	Licence to manufacture for experimental purpose is required under chapter-II, Rule 3(v) & 21 of Schedule-G of LRA Rules 1976 is required for manufacture of Investigational Medicinal Product (IMPs).	GMP certificate of the Searle Company limited is attached. (Page 339/corr.)
04	Provided adverse event reporting form is not as per CIOMS format.	CIOMS form for ADRs reporting is attached. (Page 341-342/corr.)
05	Undertaking on Stamp paper is not provided.	Undertaking on Stamp paper is now provided. (Page 343/corr.)
06	---	Sample analysis report issued by Industrial Analytical Center, H.E.J. Research Institute of Chemistry, ICCBS, University of Karachi is attached. (Page 344/corr.)

09. After evaluation following shortcomings have been observed:

i. Proposed Investigational Medicinal Product "Dietary Herbal Health Supplement-I (DHA-I)" belongs to Health & OTC product as per DRAP Act 2012 & SRO 412(I)/2014. Whereas submitted manufacturing licence of M/s The Searle Company limited is for allopathic drugs only (by way of formulation).
ii. MoU between research organization & the manufacturer is not provided.
iii. Applicant may be asked to provide manufacturing licence & GMP certificate of any enlisted manufacturer for the Health & OTC product along with MoU between research organization & manufacturer.

10. Accordingly, shortcoming letter issued on 01st July, 2021. Reply form Prof. M. Iqbal Choudhry, Director ICCBS-University of Karachi, Karachi, on 31st August 2021. Applicant response for shortcomings is as follows:

S.No.	Shortcomings	Reply
01	Proposed Investigational Medicinal Product "Dietary Herbal Health Supplement-I (DHA-I)" comes under Health & OTC product as per DRAP Act 2012 & SRO 412(I)/2014. Whereas submitted manufacturing licence of M/s The Searle Company limited is for allopathic drugs only (by way of formulation). It is hereby requested to provide Form-06 of any enlisted firm for Health & OTC products.	Not provided.
02	MoU between research organization & the manufacturer of Health & OTC product is not provided.	Attached MoU between ICCBS & The Searle Company are expired & are not for manufacturing of IMPs for subject clinical trial.
03	Enlistment certificate as manufacturing of Health & OTC product & GMP certificate of that enlisted manufacturer for the Health & OTC product need to be provided.	Not provided.

11. After re-evaluation of submitted documents following shortcomings were observed:

i. None of form-06 has been provided yet as claimed in covering letter.
ii. Details of application submission & issuance of shortcoming letter are misleading as first letter was issued on 13th April 2021, whereas second letter was issued on 01st July 2021.
iii. Provided MoU are expired and are not related to manufacture of IMPs for the applied clinical trial.
iv. Form-06 & GMP certificate of the manufacturer are not provided.

12. Accordingly, shortcoming letter again issued on 30th September, 2022. Reply from Prof. M. Iqbal Choudhry, Director ICCBS-University of Karachi, Karachi, received on 15th February 2022. Applicant response for shortcomings was as follows:

S.No.	Shortcomings	Reply	Remarks
01	Proposed Investigational Medicinal Product "Dietary Herbal Health Supplement-I (DHA-I)" comes under Health & OTC product as per DRAP Act 2012 & SRO 412(I)/2014.	Form-06 (Enlistment) certificate number 01163 of M/s The Searle Company Limited (Searle	---

	Whereas submitted manufacturing licence of M/s The Searle Company limited is for allopathic drugs only (by way of formulation). It is hereby requested to provide Form-06 of any enlisted firm for Health & OTC products.	Healthcare) F-319, SITE, Karachi.	
02	MoU between research organization & the manufacturer of Health & OTC product is not provided.	MoU between ICCBS & The Searle Company, Karachi dated 26th March 2018 valid for two years is attached.	Attached MoU is expired on 25th March 2020 & the MoU is between ICCBS & The Searle Company Karachi instead of M/s The Searle Company Limited (Searle Healthcare) F-319, SITE, Karachi.
03	Enlistment certificate as manufacturing of Health & OTC product & GMP certificate of that enlisted manufacturer for the Health & OTC product need to be provided.	GMP Certificate No. 40/2021-DRAP(K)-Health & OTC, dated 03rd November 2021 for M/s. The Searle Company Limited (Searle Healthcare) located at F-319. SITE. Karachi0Pakistan. Enlistment No.01153	---

13. After re-evaluation of submitted documents following shortcomings were observed:

i. Provided MoU is expired and are not related to manufacture of IMPs for the applied clinical trial.

ii. Attached MoU was expired on 25th March 2020 & the MoU is between ICCBS & The Searle Company Karachi instead of M/s The Searle Company Limited (Searle Healthcare) F-319, SITE, Karachi. It is advised to provide a valid MoU between M/s ICCBS, Karachi & M/s The Searle Company Limited (Searle Healthcare) F-319, SITE, Karachi, with clear term & conditions (for manufacture of IMPs for subject trial).

14. Accordingly, observed shortcomings were communicated on 28th February, 2022.

15. Reply from Prof. M. Iqbal Choudhry, Director ICCBS-University of Karachi, Karachi, received on 18th March, 2022.

16. Applicant response for shortcomings is as follows:

S.No.	Shortcomings	Reply	Remarks
01	Provided MoU is expired and are not related to manufacture of IMPs for the applied clinical trial.	Agreement between M/s Dr. Panjwani Center for Molecular Medicine and Drug Research (PCMD), Center for Chemical and Biological Sciences (ICCBS), University of Karachi	---

		and M/s The Searle Company Limited (Searle Healthcare) F-319, SITE, Karachi, dated 14th March, 2022 (valid for 04 years), for manufacture of IMPs for subject Clinical Trial is attached.	
02	Attached MoU was expired on 25th March 2020 & the MoU is between ICCBS & The Searle Company Karachi instead of M/s The Searle Company Limited (Searle Healthcare) F-319, SITE, Karachi. It is advised to provide a valid MoU between M/s ICCBS, Karachi & M/s The Searle Company Limited (Searle Healthcare) F-319, SITE, Karachi, with clear term & conditions (for manufacture of IMPs for subject trial).	-do-	---

17. After re-evaluation of the dossier it is observed that, applicant/PI possess a non-medical background & having a D.Sc. & Ph.D. in Chemistry, the matter need discussion & guidance from expert members of the CSC, in this regard the matter need to be placed before CSC. Further, it is requested that, as applied site is not a health care facility, so, it is suggested that, a trial specific inspection may be carried out to verify available facilities at the proposed site & its status (primary, secondary & tertiary care facility) & its feasibility for the subject trial.

18. Secretary CSC presented the case the case before & 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. *Committee asked to submit complete composition of DHS-I.*
ii. *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 information/reply 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. 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.

AGENDA ITEM XVII:

AMENDMENT IN NUMBER OF SUBJECTS TO BE ENROLLED IN CLINICAL TRIAL 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-DD (PS)

It is submitted that, the subject application 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 approve the Clinical Trial 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 (SEQIRUS)", under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site(s):

Clinical Trial Site(s)	**PI/Co-PI**
Aga Khan University Hospital, Karachi	Dr. Fatima Mir (National-PI)
Shifa International Hospital, Islamabad.	Dr. Ejaz A. Khan, Site-PI
Avicenna Medical college and Hospital, Lahore.	Dr. Aneela Zareen, Site-PI
Central Park Teaching Hospital, Lahore.	Dr. Muhammad Fakharul Zaman, Site-PI
Al-Shifa Trust Eye Hospital, Islamabad.	Dr. Ume Sughra, Site-PI

2. Accordingly, registration letter CT-0039 was issued on 21st October, 2022 & allowed to enroll 398 Subjects along with import of following IMPs:

i. Quantity of IMPs required along with justification:

IMPs	**Molecule**	**Strength**	**Pack Size**	**Manufacturer**	**No. of Patients**	**Per Patient Does**	**Frequency**	**TOTAL**
Active – Flucelvax Quadrivalent (QIVc)	Cell-derived season Quadrivalent influenza vaccine	Total of 60 µg hemagglutinin (HA) per 0.5m1 does in the recommended ration of 15 µg HA of each of the four (4) influenza strains recommended by WHO for inclusion in the quadrivalent vaccine formulation for the influenza season corresponding to the season of conduct of the study	1 Pre-filled Syringe (PFS) 0.5ml per kit.	Seqirus Inc., 475 Green Oaks Parkway, Holly Springs, NC 27540, United States.	199	2	1	100x2=398
Placebo - Saline	Isotonic Sodium Chloride Solution	Isotonic Sodium Chloride Solution 0.9% 0.5m1 single dose be administered	1 ampoule 10ml per kit (one single dose of 0.5ml	B. Braun Melgungen AG Mistelweg 2, 12357	199	1 Dose of Saline	28 Days	199x1=199 199x1=199

			to be administered -ampoule to be discarded after the single dose is withdrawn)	Berlin, Germany.		at Visit 2		(Each of NeisVac-C and Saline)
Comparator - NeisVac-C		10 µg of meningococcal group C polysaccharide conjugated with 10 to 20 µg of tetanus toxoid protein, absorbed to aluminum hydroxide (1.4 µg equivalent to 0.5 µg aluminum), plus the following ingredients: sodium chloride and water (4.1 µg for injection, Qs to 0.5ml)	1 Pre-filled Syringe (PFS) 0.5ml per kit	Pfizer Manufacturing Belgium NV, Rijksweg 12, BE-2870 Purus, Belgium	199	1 Dose of NeisVac at Visit 1	28 Days	199x1=199 199x1=199 (Each of NeisVac-C and Saline)

Wastage and Damage %will be 25%:
Active: 398 x 25% = 100; Total Import Quantity: 398 + 100 = 498
Placebo: 199 x 25% = 50; Total Import Quantity: 199 + 50 = 249
Comparator: 199 x 25% = 50; Total Import Quantity: 199 + 50 = 249

3. Now an application (FR, Page 989 – 1005/Corr.) (Attachment 12) 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 08th November, 2022, received on 16th November, 2022. Wherein request has been made for extended recruitment timelines. Fee challan of Rs. 25,000/- is attached but can't be verified online. Request is reproduced as under:

Respected Dr. Noor Muhammad,

With reference to DRAP approval F.No.03-11/2022-DD (PS) the phase III influenza vaccine study, protocol V130_14 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 Administrated in Healthy Subjects aged 6 Months through 47 Months.

It is to notify that several sites started enrollment later than anticipated, Seqirus has extended the enrolment period through 15th December 2022. The Principal Investigators of Pakistan concur that the influenza season is expected to last till the end of the year 2022 therefore increasing both the recruitment timeline & the recruitment target would benefit the Pakistani population at large. Especially owing to the fact that this is not a strictly placebo-controlled trial it will be extremely beneficial for the Pakistani population to receive the vaccination coverage be it the Flucelvax Quadrivalent (QIVc) or the Neisvac-C as described in the protocol.

Moreover, we wish to notify that we secured approval for 398 subjects on 14th October 2022 and would appreciate the approval of an additional 352 subjects to meet the requirement of the revised recruitment target of 750 subjects set by Seqirus for Pakistan.

The inclusion of Pakistan in the NH2022 season will bring an important geographical diversity to the study's dataset and will be key in supporting the endpoints of this trial.

4. Applicant submitted following documents:

- **i.** Life insurance coverage letter by EFU Pakistan, from AON Life Sciences, dated 28th October, 2022.
- **ii.** CSL Seqirus letter regarding "Enrollment period for the Northern Hemisphere 202212023 influenza season will be extended through 16th December, 2022".
- **iii.** Justification for Quantity of Investigational Product to be imported for Clinical Trial in Pakistan.
- **iv.** Drug Import License (Computerized No: K-1150525082578) Valid upto 30th October, 2024. (Page 996-997/Corr.)
- **v.** Certificate of Liability Insurance (Page 998-995/Corr.)

vi. Copy of Clinical Trial registration certificate (Page 999-1003/Corr.)

vii. Online/e-transaction receipt for Rs.25000/-, dated 08th November, 2022. (IQVIA Solution Pakistan have transferred Rs. 25000/- to DRAP Account IBAN: 01170010008463700018).

viii. Copy of unpaid challan No. 21260092114 (Not verified online).

ix. Prescribed fee for Miscellaneous request is paid vide challan No. 21260092114, dated 21st November, 2022.

5. According to above mentioned request for increase in enrollment:

i. Quantity of IMPs required along with justification:

Previously approved quantity of IMPs	Quantity of IMPs along with enrolments for approval
Subjects: 398 Wastage and Damage %will be 25%: Active: 398 x 25% = 100; Total Import Quantity: 398 + 100 = 498 Placebo: 199 x 25% = 50; Total Import Quantity: 199 + 50 = 249 Comparator: 199 x 25% = 50; Total Import Quantity: 199 + 50 = 249	Subjects: 750 Wastage and Damage %age will be 25% Active: 750 x 25% = 188; Total Import Quantity: 750 + 188 = 938 Placebo: 375 x 25% = 94; Total Import Quantity:375 + 94 = 469 Comparator: 375 x 25% = 94; Total Import Quantity 375 + 94 = 469

6. It is informed that, trial enrolment size will remain 3083 subjects globally & it is requested to increase the enrolment in Pakistan from 398 Subjects to 750 Subjects.

7. The Secretary CSC presented the case before CSC & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and deliberation decided to approve the increase in the enrolment in Pakistan from 398 Subjects to 750 Subjects & following revised quantities of IMPs to be imported for the trial:

IMPs	Molecule	Strength	Pack Size	Manufacturer
Active – Flucelvax Quadrivalent (QIVc)	Cell-derived season Quadrivalent influenza vaccine	Total of 60 µg hemagglutinin (HA) per 0.5m1 does in the recommended ration of 15 µg HA of each of the four (4) influenza strains recommended by WHO for inclusion in the quadrivalent vaccine formulation for the influenza season corresponding to the season of conduct of the study	1 Pre-filled Syringe (PFS) 0.5ml per kit.	Seqirus Inc., 475 Green Oaks Parkway, Holly Springs, NC 27540, United States.
Placebo - Saline	Isotonic Sodium Chloride Solution	Isotonic Sodium Chloride Solution 0.9% 0.5m1 single dose be administered	1 ampoule 10ml per kit (one single dose of 0.5ml to be administered-ampoule to be discarded after the single dose is withdrawn)	B. Braun Melgungen AG Mistelweg 2, 12357 Berlin, Germany.
Comparator - NeisVac-C		10 µg of meningococcal group C polysaccharide conjugated with 10 to 20 µg of tetanus toxoid protein, absorbed to aluminum hydroxide (1.4 µg equivalent to 0.5 µg aluminum), plus the following ingredients: sodium chloride and water (4.1 µg for injection, Qs to 0.5ml)	1 Pre-filled Syringe (PFS) 0.5ml per kit	Pfizer Manufacturing Belgium NV, Rijksweg 12, BE-2870 Purus, Belgium

Quantity of IMPs along with enrolments
Subjects: 750 Wastage and Damage %age will be 25% Active: 750 x 25% = 188; Total Import Quantity: 750 + 188 = 938 Placebo: 375 x 25% = 94; Total Import Quantity:375 + 94 = 469 Comparator: 375 x 25% = 94; Total Import Quantity 375 + 94 = 469

AGENDA ITEM XVIII:

REQUEST FOR APPROVAL AND REGISTRATION OF BIOEQUIVALENCE STUDY OF RAHMACIN (CLARITHROMYCIN) 250 MG / 5 ML SUSPENSION MANUFACTURED BY M/S MEDISURE LABORATORIES (PVT) LIMITED, KARACHI. F. No. 14-12/2021 DD (PS)

Application is from Dr. Sadia Asim, Director, Institute of Biological & Pharmaceutical Sciences (IBBPS), Dow University of Health Sciences, Ojha Campus Karachi, for approval of subject Bioequivalence Study, under the Bio-Study Rules, 2017, S.R.O.697/(I) 2018 along with prescribed processing fee of Rs.200000/- deposited vide challan number 1932889, dated 08th April 2021.

2. The summary of the proposed study is as under;

i. **Study title:** A Single-dose, Randomize, Open-Label, two-period, two-sequence, two-treatment, 2 x 2, crossover bioequivalence study Rahmacin® 250mg/5ml suspension compared with Klaricid® 250mg/5ml suspension in 26 healthy adult human subjects, under fasting condition.
ii. **Purpose of study:** To determine the Bioequivalence of Clarithromycin test product (Rahmacin 250mg/5ml Suspension) manufactured by M/s Medisure Laboratories Pakistan (Pvt) Ltd, compared with reference product (Klaricid 250mg/5ml Suspension) manufactured by Abbott Laboratories in healthy adult human subjects under the fasting condition.
iii. **Investigational Product:** Rahmacin® (Clarithromycin) 250mg/5ml Suspension of M/s Medisure Laboratories Pakistan (Pvt.) Ltd., Karachi.
iv. **Reference Product:** Klaricid® (Clarithromycin) 250mg/5ml Suspension of M/s Medisure Laboratories Pakistan (Pvt.) Ltd., Karachi.
v. **Sponsor:** M/s Medisure Laboratories Pakistan (Pvt.) Ltd., Karachi.
vi. **Principal Investigator:** Dr. Aftab A. Ali Mukhi (PI)
vii. **Co-Principal Investigator:** Dr. Javaria Choudhry & Dr. Sadia Asim.
viii. **Funding Source**: M/s Medisure Laboratories Pakistan (Pvt.) Ltd., Karachi.
ix. **Cost of the Project**: Provided.
x. **Subjects enrolment**: 26 Subjects will be enrolled in the study.

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

S. No.	Document	Remarks
1	Application on prescribed form-IIA.	Application on Form – IIA is provided.
2	Prescribed processing fee	Processing fee of Rs.200000/- deposited vide challan number 1932889, dated 08th April 2021.
3	Name of Investigational Product (including all available names; trade, generic or INN name, chemical code, etc.,)	Attached
4	Dosage Form of Investigational Product	Attached
5	Formulation of Investigational Product	COA of the Product attached.
6	Pharmacodynamics and Pharmacokinetics of Investigational Product	Attached. *Need to be reviewed by CSC experts.

7	Purpose of study defining the indication along with the anticipated cost of the project and sources of fund	To determine the Bioequivalence of Clarithromycin test product (Rahmacin 250mg/5ml Suspension) manufactured by M/s Medisure Laboratories Pakistan (Pvt) Ltd, compared with reference product (Klaricid 250mg/5ml Suspension) manufactured by Abbott Laboratories in healthy adult human subjects under the fasting condition.
8	Proposed center for the study	BA/BE Studies Center at Institute of Biological & Pharmaceutical Sciences (IBBPS), Dow University of Health Sciences, Ojha Campus Karachi,
9	Investigational design and study plan	A Single-dose, Randomize, Open-Label, two-period, two-sequence, two-treatment, 2 x 2, crossover bioequivalence study Rahmacin® 250mg/5ml suspension compared with Klaricid® 250mg/5ml suspension in **26 healthy adult human subjects**, under fasting condition.
10	Pre-clinical or clinical data or safety studies	Attached. *Need to be reviewed by CSC experts.
11	Final protocol	Protocol Number: IBBPS-012-CLA-2021/Protocol/1.0 Attached.
12	Detail of the investigator (Principal investigator, analysts, and others along with CV)	CVs of the following are attached: Dr. Aftab A. Ali Mukhi (PI) Dr. Javaria Choudhry (Co-PI) Dr. Sadia Asim (Co-PI)
13	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Copy of IRB approval, Ref: IRB-198/DUHS/Approval/2021, dated 27th March 2021 is attached. * IRB approval is for one year.
14	Approval of National Bio-ethics Committee (NBC)	Copy of NBC approval, Ref. No.4-87/NBC-617/21/61 dated 15th July 2021 is attached
15	Site approval by the Ethics committee	Attached.
16	Informed consent (English and Urdu)	Attached.
17	Summary of the protocol or synopsis (Investigational Product)	Attached.
18	Adverse Event Reporting Form	Attached.
19	Name of the monitor or clinical research associate	Muhammad Ibrar Ahmad Khan (CV attached)
20	Evidence of registration in the country of origin (GMP certificate along with CoPP or Free sale certificate)	Copy of GMP Certificate for M/s Medisure Laboratories Pakistan (Pvt) Ltd, Karachi is attached. Whereas, GMP Certificate for M/s PT. ABBOTT Indonesia, Marketing Authorization holder (Imported &

		Distributed by): Abbot Laboratories, Philippines.is not provided.
21	Copy of registration letter if registered in Pakistan	Copy of registration letter for Rahmacin (Clarithromycin) 250mg/5ml Suspension M/s Medisure Laboratories Pakistan (Pvt) Ltd, Karachi is attached. Whereas, registration letter of Klaricid® (Clarithromycin) 250mg / 5ml Suspension of M/s Abbott Laboratories Pakistan is not provided.
22	The proposed label of investigational product	Attached.
23	Quantity of investigational product to be used in the study along with justification (Note: All the quantities of the each of investigational product should be procured from one single source)	Attached.
24	Undertaking on affidavit	Attached.

4. After initial scrutiny following shortcomings were communicated to the applicant again & again but applicant informed that they are unable to provide evidence of registration, CoPP & GMP Certificate for the reference product.

5. Applicant submitted reply as follows:

S.No.	Shortcomings	Reply
01	BA/BE Study Center approval letter copy is not attached.	Provided in attachment.
02	Registration letter & GMP Certificate of Klaricid® (Clarithromycin) 250mg / 5ml Suspension of M/s Abbott Laboratories Pakistan is not provided.	Please note that Bioequivalence study will be submitted to exporting countries regulatory authorities, currently sponsor has the intention to submit the Bioequivalence study Rahmacin suspension 250mg/5ml in FDA Philippines. As per FDA Philippines Reference product Klaricid (Clarithromycin) 250mg / 5ml Suspension should be registered and Marketed in Philippines, because of that product has been procured from the Philippines market. Therefore, it is difficult to obtain Registration letter & GMP certificate of M/s Abbott Laboratories Philippines.
03	Clarification regarding formulation is required, as formulation furnished is **Clarocin** Suspension 250mg/5ml (70ml), whereas investigational product to be tested is **Rahmacin** Dry Suspension 250mg/5ml.	Please note that both Clarocin Suspension Rahmacin 250mg/5ml dry 250mg/5ml has same formulation. Batch formulas are also attached Suspension for your reference. Also note that Clarocin Suspension 250mg/5ml is locally registered brand name whereas Rahmacin dry Suspension 250mg/5ml is an approved brand name for export.
04	Complete Registration letter need to be provided.	Provided in attachment.
05	Label of Reference product are not provided.	Provided in attachment.

06	Quantity of test & reference product according to dose(s) to be used in the study need to described.	Provided in attachment.
07	Cost of the project is not described	Provided in attachment.

6. In view of above, it is informed by the applicant that, they are unable to produce CoPP of reference product & GMP Certificate of reference product manufacturer, as required under the Bio-Study Rules 2017.

7. The application was placed before CSC in its 34th meeting held on 13th January, 2022 & the CSC decided as follows:

Decision:

"The CSC after detailed discussion and deliberation decided to defer the case for fulfillment of following prerequisites as per Form-IIA of the Bio-Study Rules:

i. CoPP of reference product (i.e. Klaricid® (Clarithromycin) 250mg/5ml Suspension of M/s PT. ABBOTT Indonesia).
ii. GMP Certificate of reference product manufacturer (i.e. M/s PT. ABBOTT Indonesia)".

8. Accordingly, decision of the Committee was communicated to applicant vide letter bearing number F.No.16-34/2022 DD (PS) & F.No.14-12/2022, dated 14th January 2022 & 01st February 2022 respectively.

9. Applicant reply is reproduced as under:

Reference to the letter received on 1't February 2022 (F. No.14-1212020 - DD (PS)), regarding the fulfillment of prerequisites i.e. CoPP and GMP certificate of reference product manufacturer on application for the Bioequivalence Study of Rahmacin (Clarithromycin) 250m9/5ml suspension, We M/s Institute of Biological Biochemical & Pharmaceutical Sciences hereby enlightens the Clinical Study Committee that we have intimate the sponsor regarding the requirement of CoPP and GMP certificate of reference product manufacturers but unfortunately sponsor did not found any way to arrange the required documents.

ln order to fulfill the requirement of CSC committee we explore the web portal of National Agency for Drug and Food Control of Indonesia or Badan POM or BPOM & FDA Philippines there we found that M/s PT. ABBOTT Indonesia is registered & marketing their products in said drug regulatory agencies, we also found the evidence of clarithromycin product registration in both said drug regulatory agencies links & screenshots are provided for you reference:

Evidence of Product Registration in NADFC Indonesia:
https://cekbpom.pom.go.id//home/produUb78hom8v2h651vi9iilvivali3/all/row/1O/page/2/order/4/DESC/search/S/clarithromycin

Evidence of PT. ABBOTT Indonesia Registration in NADFC Indonesia:
https://cekbpom.pom.qo.id//home/sarana/b78hom8v2h651vi9iilvivali3/idi001.OBD-2794.05

Evidence of ABBOTT LABORATORIES Registration in FDA Philippines:
https://verification.fda.gov.ph/DRUG_TRADEReview.php?showdetail=&ACCOUNTCODE=CDRR-NCR-DT-35827

Evidence of Product Registration in FDA Philippines:
https://verification.fda.qov.ph/druq_productslist.php?cmd=search&t=drug_products&psearch=CLARITHROMYCIN&psearchtype=

Hoping that above clarification & evidences will suffice the requirement of CSC committee for the grant of Approval & Registration of Bioequivalence Study of Rahmacin (Clarithromycin) 250mg/5ml suspension.

10. It is submitted that, CoPP & GMP Certificates for test & reference IMPs is a legal requirement as per Form-II of the Bio-Study Rules 2017.

11. Secretary CSC presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of all prerequisites as per Form-IIA of the Bio-Study Rules, 2017. Further, applicant is directed to provide the said requisite documents within 30 days positively, failing which the application is liable to be rejected.

12. Accordingly, decision was communicated to applicant vide letter bearing number F.No.16-34/2022-CSC, dated 14th October, 2022.

Respected Sir,
Reference to the letter F. No 16-35/2022 - DD (P.S) dated "l4th October 2022, regarding the Bioequivalence Study of Rahmacin (Clarithromycin) 250m9/5ml suspension manufactured by M/s. Medisure Laboratories (Pvt) Limited, We M/s Institute of Biological Biochemical & Pharmaceutical Sciences hereby inform the clinical study committee of Drug Regulatory Authority of Pakistan that we have fulfilled all the prerequisites as per Form - IIA of the Bio-study Rules 2017 except CoPP & GMP certificate of Reference product.

Sponsor has tried their best to arrange CoPP & GMP certificate of reference product but they are unable to provide CoPP & GMP certificate of reference product. As per the requirement of WHO, ICH & other stringent Regulatory Authority (SRA) counties CoPP & GMP certificate of reference products are not the prerequisites for Bioequivalence studies, because reference products label is granted to only those products whose quality, efficacy & manufacturing practices are well established.

Here we are looking guidance from Clinical Study Committee (CSC) of Drug Regulatory Authority of Pakistan regarding this matter as many of our submitted applications for the conduct of Bioequivalence studies are deferred because of this requirement.

13. The Secretary presented the case before CSC & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case till submission of requisites documents (i.e. CoPP Certificate of Comparator product) as per Form-IIA of the Bio-Study Rules, 2017.

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

AGENDA ITEM XIX:

APPLICATION FOR APPROVAL OF M/S INTEGRATED MEDICAL CARE HOSPITAL, LAHORE TO ACT AS GENERALIZED CLINICAL TRIAL SITE FOR PHASE-I, II, III & IV CLINICAL TRIALS. F. NO.15-15/2022 DD (PS) F. No.15-15/2022-DD (PS)

Application is, from Dr. Muhammad Tayyib, Chief Executive Officer, having CNIC#35201-878907-9, of M/s Integrated Medical Care, Hospital (IMC) Hospital, 153/1-Street # 6 Sector-F, Phase 5, DHA Lahore, dated 24TH June, 2A22, along with fee of Rs. 100,000/- deposited

vide challan number 16il91973, dated 21-06-2022 to act as Clinical trial site for Phase I, II, III & IV clinical trials.

2. After initial evaluation as per prerequisites of Form-l of the Bio-Study Rules 2017, 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	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).	FBR Certificate or AOP certificate is not attached, only Partnership deed is attached. Whereas certificate from Punjab Healthcare Commission No REG.No-R-7094 1 is attached. IRB notification attached with the signature of applicant which is a conflict of interest.
4	Details of premises including layout plan of the site.	Complete layout of Hospital is attached instead of Specific area/site for Clinical trial site.
	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	List of Hospital Inventory attached, however equipment and machinery required for the analytical or bio-analytical and clinical studies are not provided
5	Names and qualifications of the above sections along with their staff.	CV of Muhammad Sheraz Raza, Dr. Naeem Uddin Mian, Mehwish Zahra Zaidi, Dr. Sarosh Iqbal, M. Shehzad Haq, Rana Muhammad Qasim Khan, Dr. Mariam Iqbal are attached all are IRB member's CVs of trial related staff is required to be submitted.
6	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	SOPs for emergency handling, ambulatory services and details of allied facility, ambulatory services, and emergency handling are not provided, only agreement with M/s 3R & Incinero Waste Management Company is attached.
	Undertaking	Not attached

3. After evaluation, following shortcomings were found:

i. 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 names and addresses of its partners and in the case of company the name and address of the company and its directors) (Legal Document FBR/Registrar of firm etc.).
ii. Complete layout of Hospital is attached instead of specific area/site for Clinical Trial site.
iii. List of Hospital Inventory provided, however equipment and machinery required for the analytical or bio-analytical and clinical studies are not provided.
iv. CV of Muhammad Sheraz Raza, Dr. Naeem Uddin Mian, - Mehwish Zahra Zaidi, Dr. Sarosh lqbal, M Shehzad Haq, Rana Muhammad Qasim Khan, Dr. Mariam lqbal are attached that required to be submitted.
v. Undertaking on stamp paper is not provided.
vi. Soft copy of application required for onward submission to CSC.

4. Accordingly, shortcoming letter has been issued on 01st July, 2022.

5. Reply in response to letter issued by the Division, the evaluation of reply is as under: -

Deficiencies	**Reply of applicant**
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 names and addresses of its partners and in the case of company the name and address of the company and its directors) (Legal Document FBR/Registrar of firm etc.).	Applicant has only provided the names & addresses of partners, partnership deed and addendum however legal status of the firm/hospital is not provided i.e. registration from SECP/Registrar of firms and valid registration letter from Punjab Health Care Commission.
Complete layout of Hospital is attached instead of specific area/site for Clinical Trial site.	Applicant has provided the layout plan in which area to conduct clinical trial is randomly assigned and same area is being used for general hospital patients and clinical trial. But no dedicated area is assigned for clinical trial unit which requires clarification.
List of Hospital inventory provided, however, equipment and machinery required for the analytical or bio-analytical and clinical studies are not provided.	Applicant has provided the list of equipments that are not as per approved list of equipment and machinery required for the analytical or bio-analytical and clinical studies.
CV of Muhammad Sheraz Raza, Dr. Naeem Uddin Mian, Mehwish Zahra Zaidi, Dr. Sarosh Iqbal, M Shehzad Haq,' Rana Muhammad Qasim Khan, Dr. Mariam Iqbal are attached that all are IRB members, however, CVs of trial related staff is required to be submitted.	CVs of Hafiz Muhammad Sajid, Hassan Rashid, Dr. Mehru Nisa Nadeem, Beenish Ambreen, Dr. Zunaira, Sadia Parveen, Izhaq Masih, Nadia Liaqat, Sehrish Ramzan, Sajida Bano, are attached, however, Pharmacist involved in handling of IMP is not mentioned.
Undertaking on stamp paper is not provided.	Provided

6. Reference to the reply submitted by the applicant, it is observed that, the proposed site is not equipped with facilities required for Pharmacokinetics / Pharmacodynamics assays, as required in Phase-I / Phase-II Clinical Trials. So, it was proposed that, the site may be inspected for Phase-III & Phase-IV Clinical Trials only, if agreed please.

7. Accordingly, following expert panel constituted by Chairman CSC for inspection of the site for Phase-III & Phase-IV Clinical Trials only (letter issued on 27th October, 2022): -

i.	**Dr. Javed Akram,** Ex-VC, University of Health Sciences, Lahore.
ii.	**Mr. Ajmal Sohail Asif,** Director, QA & LT Division, DRAP.
iii.	**Waqas Latif,** (Member CSC)Bio-Statistician, U.H.S., Lahore.
iv.	**Rana Ahsan Ul Haq Athar, (Coordinator)** Deputy Director, Pharmacy Services Division-DRAP.

8. Nominated Experts panel inspected the subject site on 07th November, 2022 & submitted inspection report with following remarks:

The panel visited the M/s IMC Hospital, the proposed PI i.e. Dr. Qasim Rana was not present. No storage for IMPs available. There was no proper CTU present. The panel decided to defer the site for improvements. Hence recommended to defer for improvements.

- **Deferred for improvements.**

9. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and in light of expert inspection panel recommendations decided to defer the case for further improvements. The applicant is directed to submit compliance report not later than 30 days.

Further, the Committee delegated the power to the Chairman CSC for constitution of the inspection panel to visit the site and reconfirm the requirements/improvements.

AGENDA ITEM XX:

APPLICATION FOR THE RENEWAL OF LICENCE OF M/S DRK PHARMA SOLUTION TO ACT AS CONTRACT RESEARCH ORGANIZATION (CRO) (F. No.03-13/2017-DD (PS))

The case is an application from Asim Munir, CNIC:35202-4375948-5, General Manager of M/s DRK Pharma Solutions Pvt Ltd 1st Floor, Building No. 1, The Enterprise, 15km Multan Road, Lahore, Pakistan, wherein they have requested for renewal of license act as Clinical Research Organization (CRO) which expires on 10th October, 2022 (Page 166/Corr.) along with prescribed fee of Rs 300,000 submitted vide challan No. 761529554421 dated14-09-2022.

2. The application evaluated according to pre-requisites as mentioned in Form-III of the Bio-Study Rules notified vide SRO 697(I)/2018, 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 300,000 submitted vide challan No. 761529554421 dated14-09-2022.
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	The company is registered with SECP with Corporate Universal Identification No. 0104337 .
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.	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. The applicant has submitted the pre-requisites as per checklist approved by CSC under Bio-Study Rules 2017. Accordingly, following panel was constituted for inspection of the M/s DRK Pharma Solution;

1. The Director, Division of Pharmacy Services, DRAP, Islamabad.
2. The Additional Director, DRAP, Lahore.
3. Assistant Director (V), Division of Pharmacy Services, DRAP, Islamabad.

4. The panel comprising of Dr. Noor Muhammad Shah, Director, DRAP, Islamabad, Mist Majida Mujahid, Additional Director, DRAP, Lahore and Mr. Muhammad Ansar, Deputy Director, DRAP Islamabad, conducted the inspection of M/s DRK Pharma Solution, Lahore on 20.10.2022 and recommended the renewal for approval with following remarks;

The firm is involved in number of trials. some of which are still ongoing, have employed no. of technical persons for onsite quality assurance function and have positive attitude towards improvement as per new guidelines and the panel recommended for renewal of licence to act as CRO.

5. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and in light of expert inspection panel recommendations decided to approve the case of renewal of the licence of M/s DRK Pharma Solutions, Lahore to act as Contract Research Organization.

AGENDA ITEM XXI:

APPLICATION FOR LICENCE TO ACT AS CONTRACT RESEARCH ORGANIZATION (CRO) AT M/S ORCI TRIALS (PVT), LIMITED, LAHORE. (F. No.15-08/2022-DD (PS))

Application is from Dr. Jawad Gill (CNIC:42301-0813148-5), CEO, M/s Orci Trials Private Limited, situated at Level 5, 10-A, Phase 6C, DHA, Lahore, dated 06th April 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/- paid vide challan number 1651626062, dated 01st April 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	Prescribed fee	Rs.300000/- paid vide challan number 1651626062, dated 01st April 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 Registration No.4548055, dated 24th February 2022. • SECP Certificate of incorporation.
4	Details of premises including layout plan of the site.	Only 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	Copy attached.

3. In view of above, following panel was constituted by the Chairman Clinical Studies Committee.

i. Prof. Dr. Javed Akram, VC, University of Health Sciences, Lahore.
ii. Mrs. Majida Mujahid, Additional Director, DRAP, Lahore
iii. Rana Ahsan Ul Haq Athar, Assistant Director, DRAP, Islamabad.

4. The inspection panel inspection conducted the inspection on 21.10.2022 and has recommended the M/s ORCI Trials (Pvt.) Ltd., to act as Contract Research Organization (CRO) with following remarks;

The team presented the case in professional way. the panel suggested to strengthen the QA department and to improve SOPs. Keeping in view the professional aptitude, staff, training and commitment towards improvement, Panel recommended M/S Orci Trials to act as CRO.

5. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and in light of expert inspection panel recommendations decided to approve M/s Orci Trials (Pvt.) Ltd., Lahore to act as Contract Research Organization.

AGENDA ITEM XXII:

APPLICATION FOR LICENSE TO ACT AS CLINICAL TRIAL SITE (CTS) FROM THE CHILDREN HOSPITAL & THE INSTITUTE OF CHILD HEALTH (CH & ICH), LAHORE. (F. NO.15-18/2021 DD (PS).

The case is an application from Dr. Attia Bari, Associate Professor, Paeds Medicine, CNIC No. 35202-2594360-4 has applied for Clinical Trial Site, situated at Department of Paediatrics Medicine, The Children hospital & The Institute of Child Health (CH & ICH), Lahore. The application is on Form-I of the Bio-Study Rules 2017 with 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	Fee challan of Rs.100,000/- attached submitted vide slip No. 2013469.
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 but following details are submitted. The Children's Hospital & the Institute of Child Health, Lahore established in 1990, OPD Block was operationalized in May 1995 and emergency services were started in October 1996. The Children's Hospital has been providing inpatient services since December 18, 1998. The hospital provides a wide range of services both inpatient and outpatient, with a full backup of diagnostic services. The Institute of Child Health is providing post-graduate training to a very large number of doctors in multiple disciplines as well as conducting research projects. The department of Paediatrics medicine is one of the few departments of its kind providing preventive, promotive, and rehabilitative services to children. It provides not only indoor and outdoor services but also outreach services to families of the community attached to the department. The Children's Hospital & The Institute of Child Health, Lahore as a clinical trial site as it fulfills all the pre- requisites required by GCP guidelines. This would enable the Hospital to fulfill the civic responsibility of contributing to the advancement of medical research in the largest public interest. Locking forward to your kind and prompt response in this regard.
4	Details of premises including layout plan of the site.	Not Attached
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	**SC Room.** Infantometer, Wall fixed stadiometer, weighing scales, MUAC tape, WHZ score chart, Stretcher. **Nutrition Room.** Gas Stove, Kitchen Scale, Refrigerator, Microwave oven, measuring cup/ spoons, graduated jugs, blended utensils for mixing and preparing food. Feeding Cups, bowls, spoons.
6	Names and qualifications of the above sections along with their staff.	Attached
8	Undertaking on stamp paper	Attached.

3. The following panel was constituted by Chairman CSC/ Director Division of Pharmacy Services;

i. Prof. Dr. Nadeem Irfan Bukhari, UCP, University of the Punjab, Lahore.

ii. Prof. Dr. Javed Akram, VC, UHS/ Prof. Dr. Ali Jawa, UHS, Lahore.
iii. Dr. Farhana Badar, Bio-Statistician, SKCH&RC, Lahore.
iv. Dr. Masud Ur Rehman, Director Pharmacy Services Division, DRAP, Islamabad.
v. Mr. Irshad Hussain, Chief Pharmacist, (Co-opted member) Mayo Hospital Lahore.

4. The following panel inspected M/s The Children Hospital, Lahore, University of Child Health Sciences, Lahore on 23.04.2022.
   i. Dr. Masood Ur Rehman, The Then Director (PS), DRAP, Lahore.
   ii. Prof. Dr. Javed Akram, the then VC UHS, Lahore.
   iii. Malik Irshad Hussain, Pharmacy Council, Punjab.
   iv. Waqas Latif, Bio-Statistician, UHS, Lahore.
   v. Dr. Shah Noor, Assistant Professor, UHS, Lahore.

5. The panel has recommended the proposed CTS for approval with following remarks;

   Keeping in view, the site inspected, people met, their training, education/qualification, experience, IT room, archiving room, waste management, and incineration system, dedicated pharmacy for IMPs, SOPs and documentation, the panel recommended the CTU situated Children Hospital, University of Child Health Sciences for phase III & IV (Non-invasive) clinical trials in pediatrics.

6. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and in light of expert inspection panel recommendations decided to approve "The Children Hospital & The Institute of Child Health (CH & ICH), Lahore, to act as Clinical Trial Site for Phase-III & Phase-IV (Non-Invasive) Clinical Trials in Paediatrics only.

AGENDA ITEM XXIII:

APPLICATION FOR LICENSE TO ACT AS CLINICAL TRIAL SITE (CTS) FOR PHASE-II (TRIAL SPECIFIC) FROM M/S ABDUL WAHEED TRUST (AVICEENA DENTAL COLLEGE), LAHORE. (F. NO.15-09/2022 DD (PS).

The case is an application from Abdul Waheed Sheikh CNIC No.35201-1304557-7, Chairman, M/s Abdul Waheed Trust located at Avicenna Medical college & Hospital phase IX, DHA, Bedian road, Lahore wherein he has applied for Clinical Trial Site situated at Avicenna Medical college & Hospital, Phase IX, Bedian Road Lahore for Phase II. As per covering letter, the applicant has written that Abdul Waheed Trust is seeking approval as clinical trial site for Protocol Number TG2018V01 specific phase II site approval for trial titled as "A Global Multicenter, Randomized, Double -Blind, Parallel controlled Clinical Study to evaluate the Immunogenicity and safety of Different Production Scales and Batches of Recombinant SARS-CoV-2 Fusion Protein vaccine in Adults aged 18-59 Years". Application is on Form -I of the Bio-Study Rules 2017 with 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	Fee challan of Rs.100,000/- attached submitted vide slip No. 021275670104 dated 4th 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 addresses of its partners and in the case of company the name and address of the company and its directors).	Attached. The applicant is Chairman of the trust.
4	Details of premises including layout plan of the site.	Layout plan of Avicenna hospital, Avicenna Medical college, Avicenna dental college and Hospital, Gulfreen Nursing College and Institute of Allied Health sciences is attached. **The details of Clinical Trial Site including its layout plan is required.**
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	**Not Attached**
6	Names and qualifications of the above sections along with their staff.	**Not 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. After evaluation, it was noticed that application is from Abdul Waheed Sheikh, chairman Abdul Waheed Trust. Under the Umbrella of Abdul Waheed Trust, Avicenna Medical college, Avicenna Hospital, Avicenna dental College and hospital, Gulfreen Nursing College and Institute of Allied Health sciences are working. Applicant has attached the documents of all above mentioned institutions in his application.

4. Accordingly, following shortcomings were communicated to the applicant.

i. Where the Clinical Trial Site is located? Is it a specific site or whole Abdul Waheed Trust?
ii. The details of Clinical Trial Site including its layout plan is required.
iii. Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.
iv. CVs of Staff working in Clinical Trial Site and analytical or Bio-analytical Lab and Abdul Waheed Sheikh are required

5. In reply, the applicant did not address the above mentioned queries. As per previously submitted Form-I, the CTS is located at Avicenna Medical College, as per site MAP its located in Avicenna Dental College Building and as per clinical trial layout MAP it is Avicenna Hospital. Instead of analytical/ bio-analytical lab, applicant enclosed list of Diagnostic Lab. Applicant attached staff list working at CTU but list of staff working at analytical/ bio-analytical lab not provided.

6. Again following shortcomings were communicated with more clarity.

i. Where the Clinical Trial Site is located? Is it a specific site or whole Abdul Waheed Trust? **But as per Form-I CTS is located at Avicenna Medical college, as per site MAP it is located at Avicenna Dental College Building and as per CTS layout MAP it is at Avicenna Hospital. Please specify the Clinical Trial Site where it is located??**

i. The details of Clinical Trial Site including its layout plan is required **but still it's not clear that where CTS is located.**

iii. Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. **But you have attached the list of machinery and equipment of diagnostic lab instead of analytical or bio-analytical lab.**

iv. CVs of Staff working in Clinical Trial Site and analytical or Bio-analytical Lab and Abdul Waheed Sheikh are required **but you have not attached the CVs of staff working at analytical or bio-analytical lab.**

7. M/s Abdul Waheed Trust in response to this office letter submitted the reply wherein applicant has stated that;

i. Abdul Waheed Trust and all its constituent institutions including: Avicenna Medical College, Avicenna Dental College, Avicenna Hospital, Gulfreen Nursing College, Institute of Allied Health Sciences and Avicenna Clinical Research Center, Student and Doctors Hostels are located on the same site of 23 acres as given in the site map earlier in Annex - A. The Clinical Trial Site Avicenna Clinical Research Center ' is located on the second floor of Avicenna Dental College block. CTS has been highlighted in yellow and labeled in Annex - A for your perusal.

ii. The details of Clinical Trial Site and its layout attached as Annex - B. Its location has been specified in para i above.

iii. For the requested Phase - II approval we have provided a justification letter (copy attached as Annex - C) regarding TG2108V01 Trial Specific Phase - II Site Approval. For this Phase - II trial standard sampling / testing will not be performed at the Clinical Trial Site and shall be outsourced as follows: a. The RT - PCR sampling is outsourced to Central Laboratory in Pakistan b. For immunogenicity testing, as per protocol; samples will be taken at site level and further investigation will be performed in the laboratory outside Pakistan. Only Blood Urine Pregnancy Test (UPT), pid IgG and testing will be performed at site level. Therefore, due the above reason, we do not need bioanalytical lab facility at the Clinical Trial Site as testing will not be performed Site. RT - PCR and immunogenicity testing will not be performed at the Clinical Trial Site and this testing will be outsourced as mentioned in point above, we do not need bioanalytical lab staff for this trial

8. As per statement of the applicant the CTS is located in Avicenna Medical College and it may be considered as trial specific for Protocol Number TG2018V01 specific phase II site approval for trial titled as "A Global Multicenter, Randomized, Double -Blind, Parallel controlled Clinical Study to evaluate the Immunogenicity and safety of Different Production Scales and Batches of Recombinant SARS-CoV-2 Fusion Protein vaccine in Adults aged 18-59 Years"

9. The following panel was constituted vide this office letter dated 7th July 2022

i. Dr. Javed Akram, VC, University of Health Sciences, Lahore.
ii. Dr. Farhana Badar, Bio-Statistician, Shaukat Khanum Hospital & Research Institute, Lahore.
iii. Ms. Majida Mujahid, Additional Director, DRAP, Lahore.
iv. Ahsan Ul Haq Athar, Assistant Director (P.S), DRAP, Islamabad.

10. The panel inspected the premises on 7th June 2022 and recommended the proposed clinical trial site with following remarks.

"Keeping in view the previously conducted studies e.g. Anhui Vaccine (ZF 001) and Livzon Booster Dose (ongoing), the panel recommend for approval the site for phase-II trial titled as "A Global, Multicenter, Randomized, Double-Blinded, Parallel controlled, clinical study to evaluate the immunogenicity and safety of different production scales and batches of Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01) in adults aged 18-59 years"

However, the committee/ panel expressed their concerns of this phase-II trial in Pakistani volunteers for booster dose when the same is available in Pakistan through Government resources free of cost and that also of superior (mRNA) Vaccine. Similarly, this panel strongly recommend that the investigator obtain clear cut recorded ICF explaining above to volunteers."

11. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC discussed the application in detail in light of recommendation of inspection panel report. It was decided to reject the case as the proposed Clinical Trial application has been withdrawn.

AGENDA ITEM XXIV:

A PHASE II/III, RANDOMIZED, DOUBLE BLINDED STUDY TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF A BOOSTER DOSE OF PIKA-ADJUVANTED RECOMBINANT SARS-CoV-2 SPIKE (S) PROTEIN SUBUNIT VACCINE IN ADULTS ≥ 18 YEARS OLD WHO RECEIVED 2 OR MORE DOSES OF INACTIVATED COVID-19 VACCINE. (F. NO.03-09/2022 DD (PS).

The case is from Prof. Dr. Aamer Ikram (51401-0924270-9), Executive Director, M/s National Institute of Health, Park Road, Chak Shahzad, Islamabad, forwarded by Dr. Syed Rooh Ul Arifeen Naqvi, Project Manager, M/s DRK Pharma Solution, Lahore, dated 26th July, 2022. Wherein request has been made for approval of subject Clinical Trial, on prescribed Form-II of the Bio-Study Rules, 2017, along with a fee of Rs. 200,000/- deposited vide challan no. 36705789611, dated 20th July, 2022. The trial details are available on U.S National Trial Registry with identification number ***NCT05463419*** *(https://clinicaltrials.gov/ct2/show/NCT05463419)*.

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

i. **Sponsor:** Yisheng Biopharma (Singapore) Pte. Ltd., Singapore.

ii. **Purpose & description of trial:** The purpose of this study is to evaluate the efficacy, safety and immunogenicity of a booster dose of PIKA COVID-19 vaccine compared to the comparator inactivated COVID-19 vaccine in adults ≥ 18 years' old who received 2 or more doses of inactivated COVID-19 vaccine.

3. In phase II, a total of 300 eligible subjects will be randomly allocated in a 1:1 ratio to receive PIKA COVID-19 vaccine or the comparator inactivated COVID-19 vaccine. The ratio of the GMT of neutralizing antibody on Day 14 after the booster dose of PIKA COVID-19 vaccine group and inactivated COVID-19 vaccine group will be calculated. Based on the Phase I immunogenicity data of PIKA vaccine, the proposed Phase II sample size results in nearly 100% power in a two-sample t test of the log- transformed neutralizing antibody titers with a two-sided alpha=0.05. Among 300 subjects, at least 200 subjects will be enrolled as subset of long-term immunogenicity and 100 subjects will be enrolled as subset of early immunogenicity. Among the 100 early immunogenicity subset, the ratio of the GMT of neutralizing antibody on Day 7 after the booster dose of PIKA COVID-19 vaccine group and inactivated COVID-19 vaccine group will be calculated. Therefore, the 100 subjects randomized to the early immunogenicity subset will have additional blood sampling on Day 7. After completion of the 7-day safety observation following the immunization of all subjects in the Phase II trial, a Safety Monitoring Committee (SMC) meeting will be held to determine whether to initiate enrollment of participants in the Phase III trial. In phase III, total 9,000 eligible subjects will be randomly allocated in a 1:1 ratio to the PIKA COVID-19 vaccine group or the comparator inactivated COVID-19 vaccine group. The sample size provides an approximately 90% power to detect a protection rate of at least 65% by PIKA vaccine in a Poisson regression analysis with a one-sided alpha of 0.025. The calculations consider an interim analysis performed with 50% of the information collected using a Pocock boundary to adjust for multiplicity. A 1% infection rate in the control group

and an approximately a 10% attrition rate are assumed. It is of note that while the actual background incidence rate can vary, the sample size requirement amounts to achieving an observation of 82 COVID-19 cases to ensure the statistical power under the 65% protection rate assumption. Similarly, the interim analysis will need to be conducted at when approximately 41 cases are observed to maintain the planned operating characteristics. Among total subjects, at least 6% subjects will be enrolled as subset of immunogenicity. Eligible subjects will receive a dose of investigational vaccine via intramuscular injection in deltoid muscle on Day 0. All subjects will be monitored for at least 30 minutes after injection. Solicited AEs will be recorded for 7 days. Unsolicited AEs and MAAEs will be recorded for 28 days following injection. SAEs, SUSARs, AESIs will be recorded for the entire duration of the study. It will take about 13 months for each subject from enrollment to the last visit. Some subjects may withdraw or discontinue from the study during the study for any reason.

iii.Arms & Interventions:

Arm(s)	**Intervention/treatment**
Experimental: PIKA COVID-19 vaccine One dose of the experimental vaccine should be administered on Study Day 0 in the deltoid muscle	Biological: PIKA COVID-19 vaccine SARS-CoV-2 spike subunit protein, PIKA adjuvant
Active Comparator: Sinopharm inactivated Covid-19 vaccine One dose of the control vaccine should be administered on Study Day 0 in the deltoid muscle.	Biological: PIKA COVID-19 vaccine SARS-CoV-2 spike subunit protein, PIKA adjuvant

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

A. Study Vaccine

Vaccine: PIKA COVID-19 Vaccine.
Dosage Form: Injection.
Composition: Each vaccine contains 5 µg amount S protein with fixed amount of PIKA adjuvant.
Route: Intramuscular injection into the deltoid muscle.

B. Control Vaccine:

Vaccine: Inactivated COVID-19 vaccine
Dosage Form: Injection
Composition: Each vaccine contains inactivated SARS-COV-2 virus
Route: Intramuscular injection into the deltoid muscle.

C. Quantity required:

Study Intervention	**Test Drug**	**Comparator**
Intervention Name	PIKA-Adjuvanted Recombinant SARS-CoV-2 Spike (S) Protein Subunit Vaccine (PIKA COVID- 19 vaccine).	COVID-19 vaccine (Vero cell) inactivated (single dose vial)
Dose Formulation	Vialed volume: 1.0 ml, Spike protein: 5 µg, PIKA adjuvant: 1.0 mg/ml, Polysorbate 80: 0.01%, Arginine hydrochloride: 140mM, Phosphate-buffered saline (PBS): Amount added depending on the final volume.	Vialed volume: 0.5ml 0.5ml dosage contains 6.5 µg of inactivated SARS-CoV-2 antigen.
Each Vial Contain	PIKA COVID-19 vaccine 1.0 ml	COVID-19 vaccine (Vero cell) inactivated 0. 5ml/vial

Quantity to be imported	165 for Phase II 1650 for Phase III Total: 1815	165 for Phase II 1650 for Phase III Total: 1815
Total box to be imported	5	To be procured locally from National Institute of Health (NIH)
Total subjects to be recruited in Pakistan	300 for Phase II 3000 for Phase III Total: 3300	

v. **Number of subjects to be recruited: 9300 Subjects (globally).** For Pakistan 300 for Phase-II & 3000 for Phase-III

vi. Study design & details:

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	9300 participants (Globally) Pakistan 300 for Phase-II & 3000 for Phase-III
Allocation:	Randomized
Intervention Model:	Sequential Assignment
Masking:	Triple (Participant, Care Provider, Investigator)
Masking Description:	Double Blind
Primary Purpose:	Prevention
Official Title:	A Phase II/III, Randomized, Double-blinded Study to Evaluate the Efficacy, Safety and Immunogenicity of a Booster Dose of PIKA Recombinant SARS-CoV-2 Vaccine in Adults Who Received 2 or More Doses of Inactivated Covid-19 Vaccine.
Estimated Study Start Date :	15th August, 2022
Estimated Primary Completion Date :	30th September, 2023
Estimated Study Completion Date :	31st December, 2023

4. The study carried out under the supervision of Dr. Aamer Ikram (National PI). The trial comprises of following primary objective(s);

i. Immunogenicity at Phase II Study [Time Frame: at day 14 after booster] Geometric mean titer (GMT) of neutralizing antibody against Omicron virus on D14 after the booster dose.

ii. Efficacy at Phase III Study [Time Frame: up to 360 days after booster] Incidence of first occurrence of Rt-PCR positive symptomatic illness after D14 of booster dose.

iii. Safety at Phase II and Phase III [Time Frame: up to 360 days after booster.] Incidence of AE, MAAE, SAE, SUSAR and AESI after booster dose.

5. Proposed Clinical Trial Site(s):

i. National Institute of Health (NIH), Islamabad.

ii. Al-Shifa Trust Research Center, Rawalpindi.

iii. Central Park Teaching Hospital, Lahore.

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.200000/- deposited vide challan number: 36705789611, dated 20th July, 2022.
3	Investigator Brochure (s)	IB for compound No. YS-SC2-010, Version: v2.0, dated: 16th June 2022 is attached. IB of comparator (COVID-19 Vaccine (Vero Cells) Inactivated) is not provided.
4	Final protocol	Attached Protocol No. YS-302 Version 1.0, dated 22nd May, 2022 * Insurance policy & its details need to be provided.
5	Informed consent and participant information sheet (Urdu to English)	Two separate ICF(s) for Phase-II & Phase-III are attached. Clarification for following need to be provided: * There is difference in translation in compensation description of Phase-III ICF. * Further details regarding insurance policy subscription is not provided.
6	List of participating countries	United Arab Emirates, Philippines & Pakistan.
7	Phase of trial.	Phase – II & Phase-III. * Application initially may be approved only for Phase-II & after submission of Phase-II results then its phase-III may be approved depending upon phase-ii results.
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 vaccine will be as follows: i. PIKA COVID-19 vaccine 1.0 ml (165 for Phase II & 1650 for Phase III) ii. COVID-19 Vaccine (Vero cell) inactivated (single dose vial) (165 for Phase II & 1650 for Phase III) * It is informed that, test drug will be imported whereas comparator will be procured locally from NIH, Islamabad, procurement procedure & details regarding purchase of comparator from NIH, Islamabad need to be provided.
9	Site of the trial	i. Al-Shifa Trust Research Center, Rawalpindi. (Site is not approved for Phase-II Clinical Trials) ii. Central Park Teaching Hospital, Lahore. (Site is not approved for Phase-II Clinical Trials) iii. National Institute of Health (NIH), Islamabad. (Site is not approved for Phase-II Clinical Trials)

		* All proposed Clinical Trial Sites(s) are not approved 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.	National Institute of Health's IRB/ERC approval, dated 14th July, 2022, without any specified time of approval is attached. 352-357 **Note:** The composition of National Institute of Health's 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 to the Bio-Study Rules, 2017. Institute is advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue approval.
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter no.4-87/COVID-110/22/, dated 07th July, 2022 (for a period of **Six** months). **Note:** As NIH's 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. **i. Prof. Dr. Aamer Ikram (PI), National Institute of Health (NIH), Islamabad. (258-322/Corr.)** **ii. Prof. Dr. Ume Sughra (Co-PI), Al-Shifa Trust Research Center, Rawalpindi. (324-339/Corr.)** **iii. Prof. Dr. Muhammad Ahmad, Central Park Teaching Hospital, Lahore. (340-349/Corr.)**
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following are attached: i. M/s Liaoning Yisheng Biopharma Co., Ltd., Shenyang China. ii. Pfizer Limited, UK. COA of following IMPs are attached: i. PIKA Recombinant COVID-19 Vaccine (CHO cell, S protein) Drug Substance, YS-SC2-010 Drug Substance. * GMP certificate of comparator's manufacturer (i.e. Beijing Institute of Biological Products Co. Ltd., China) need to be provided. ** CoPP/EUA of following need to be provided: i. PIKA Recombinant COVID-19 Vaccine (CHO cell, S protein) Drug Substance, YS-SC2-010 Drug Substance. ii. (COVID-19 Vaccine (Vero Cells) Inactivated)
14	Pre-clinical/clinical safety studies	Some articles are attached. It is informed that, Interim Analysis Report for Phase I PIKA Covid- 19 vaccine study is under preparation and will be submitted as part of the clinical trial application dossier for the applied study once

		available. Details regarding Phase-I need to be provided.
15	Summary of Protocol	Attached. As attached protocol is not finalized & signed so after its finalization & signature need to be submitted along with its summary.
16	Summary of Investigator Brochure	Summary of IB for comparator is not provided; **i.COVID-19 vaccine (Vero cell) inactivated**
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	9300 Subjects (globally). For Pakistan 300 for Phase-II & 3000 for Phase-III. * It seems that Sponsor is conducting Phase-II only in Pakistan, clarification need to be provided that, why Phase-II will not be carried out at other two participating countries.
19	Name of Monitors & Clinical Research Associate	M/s DRK Pharma Solutions (Pvt) Ltd., Lahore. Details of monitor is attached.
20	Evidence of registration in country of origin.	**Not provided.** As IMPs are not registered, Emergency Use Authorization (EUA) Certificate for all IMPs need to be provided. Further lot/batch wise COAs of IMPs need to be provided. Which will be utilized in the trial after its approval.
21	Copy of registration letter (if registered in Pakistan)	**Not provided.** As IMPs are not registered, Emergency Use Authorization (EUA) Certificate for all IMPs need to be provided.
22	Sample of label of the investigational product / drug.	Attached but labels are not as per ICH-GCP guidelines & as the study is double blinded so commercial labels or labels with IMPs name can't be used.
22	Duration of trial	The duration of participation of each individual subject is approximately 13 months from the consent to last visit. Estimated timelines for study startup, recruitment and close out activities are 5 months. Total duration of study is **18** Months
23	Undertaking on Stamp paper	Attached.

7. After initial scrutiny following shortcomings were communicated vide this office letter F.No.03-08/2022 DD (PS) were communicated to applicant:

i. Insurance details of the study is not mentioned in protocol as required by ICH-GCP Guidelines.

ii. Details regarding sample collection, storage & transportation to bioanalytical laboratory in China is not provided as proposed sites haven't facilities required for bioanalysis of collected samples required in Phase-II.

iii. Application initially may be approved only for Phase-II & after submission of Phase-II results then its phase-III may be approved depending upon phase-ii results.

iv. Details regarding comparator, its manufacturer & process/way of procurement is not clear.

v. Anticipated cost of the project is not provided.

vi. IB & summary of comparator IMPs (COVID-19 Vaccine (Vero Cells) Inactivated) is not provided.

vii. There is difference in translation in compensation description of Phase-III ICF. Further details regarding insurance policy subscription is not provided in ICF.

viii. Application is for both Phase-II & Phase-III. It may be for Phase-II only & after submission of Phase-II results then its phase-III may be approved depending upon Phase-II results.

ix. It is informed in application that, test drug (IMPs) will be imported. Whereas, comparator will be procured locally from NIH, Islamabad. Comparator procurement procedure & details regarding purchase of comparator from NIH, Islamabad need to be provided.

x. All proposed Clinical Trial Sites(s) are not approved for Phase-II Clinical Trials.

xi. The composition of National Institute of Health's IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines. So, its IRB/ERC & NBC approval for the subject trial can't be considered. Institute is 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. Then both IRB/ERC & NBC approval need to be provided.

xii. GMP certificate of comparator's manufacturer (i.e. Beijing Institute of Biological Products Co. Ltd., China) need to be provided.

xiii. CoPP/EUA of following need to be provided:

a. PIKA Recombinant COVID-19 Vaccine (CHO cell, S protein) Drug Substance, YS-SC2-010 Drug Substance.
b. (COVID-19 Vaccine (Vero Cells) Inactivated)

xiv. It is informed that, Interim Analysis Report for Phase-I, PIKA Covid- 19 vaccine study is under preparation and will be submitted as part of the clinical trial application dossier for the applied study once available. Details regarding Phase-I need to be provided.

xv. As per provided details regarding subject enrolment, it seems that Sponsor is conducting Phase-II CT only in Pakistan, clarification need to be provided that, why Phase-II will not be carried out at other two participating countries.

xvi. As IMPs are not registered, Emergency Use Authorization (EUA) Certificate for all IMPs need to be provided. Further lot/batch wise COAs of IMPs need to be provided. Which will be utilized in the trial after its approval.

xvii. Sample label are provided but labels are not as per ICH-GCP guidelines & as the study is double blinded so commercial labels or labels with IMPs name can't be used.

8. The CRO submitted reply on behalf of Major General Prof. Dr. Aamer Ikram, Executive Director National Institute of Health, Islamabad, in response to this office letter F.No.03-08/2022 DD (PS) dated 30th August 2022. The reply has been evaluated in tabulated as under;

S. No.	Shortcoming/ query	Reply	Remarks
1	Insurance details of the study is not mentioned in protocol as required by ICH-GCP Guidelines	Insurance details are provided in the study Informed Consent Form (ICF). As every subject shall keep one copy of signed ICF,	As mentioned in the reply, no document regarding insurance details is attached.

		therefore it is written in the ICF to keep the subject aware of the availability of insurance coverage in this study. Liability limit per person is PKR 2,500,000/-, quotation from insurance company is attached for your reference.	
2	Details regarding sample collection, storage & transportation to bioanalytical laboratory in China is not provided as proposed sites are not having facilities required for bioanalysis of collected samples required in Phase-II studies/trials.	For the bioanalysis, the collected samples (serum) will be shipped to the Q^2 Solutions Pte. Ltd., Singapore. The Material Transfer Agreement (MTA) between DRK Pharma Solutions (CRO), Yisheng Biopharma (Sponsor) and Q2 Solutions (Central Lab) is attached. The samples (serum) will be stored at the site (NIH) at the -20°C temperature and will be transported at the same temperature to the Q2 Solutions Pte. Ltd., Singapore.	As claimed in the reply, the Material Transfer Agreement (MTA) between DRK Pharma Solutions (CRO), Yisheng Biopharma (Sponsor) is not attached & no SOP as required is provided.
3	Application may initially be considered/approved only for Phase-II study & after submission of Phase-II results subsequently its phase-III trial may be applied afresh for consideration of the competent forum (depending upon phase-II study results).	Kindly provide the clinical trial approval for Phase II and III trial together, as the nature of trial is competitive recruitment globally for both the phases of the trial. Once the Phase II will be completed, we will submit the preliminary data analysis and Independent (Study Monitoring Committee) SMC recommendation letter to start the phase III of the trial globally. In the other participating countries (UAE & Philippines) the clinical trial approval is granted for both Phase II and Phase III (Attached for reference). In order to achieve the recruitment timelines at the same time as in UAE and Philippines, we request you to kindle give the collective approval of Phase II and Phase III with the condition	It is again informed that, as per available record none of the applied site is approved for Phase-II Clinical Trials.

		of submitting the recommendation letter from Independent SMC and preliminary data analysis of Phase II.	
4	Details regarding comparator, its manufacturer & process/way of procurement need to be clarified.	COVID-19 vaccine (Vero cell) inactivated (single dose vial) will be used as a comparator vaccine for YS-302 clinical trial which is already a marketed product by Beijing Institute of Biological Products Co. Ltd. Please find the attached CoA and EUA for the comparator vaccine. This will be procured locally from National Institute of Health (NIH) Pakistan. An agreement copy is attached for comparator procurement.	Name of the Comparator IMPs is not provided. Further, agreement for comparator product, as stated in the reply is not provided. Role of NIH, Islamabad in procurement/import of Sinopharm Vaccine is not clarified. As supply of IMPs is sole responsibility of the Sponsor, so, it is again requested to provide details regarding comparator, its manufacturer & process/way of procurement & agreement between Sponsor & manufacturer of comparator.
5	Anticipated cost of the project is not provided.	The anticipated cost for the project is USD 3,689,475 mentioned in Form II.	---
6	IB & summary of comparator IMPs (COVID-19 Vaccine (Vero Cells) Inactivated) is not provided.	Investigator brochure and summary for Investigational Product is already provided. For comparator vaccine (Sinopharm), investigator brochure, EUA and CoA is attached.	Investigator's Brochure / EUA & CoA of Comparator IMPs (Sinopharm) is not provided.
7	There is difference in translation in compensation description of Phase-III ICF. Further details regarding insurance policy subscription is not provided in ICF.	The compensation in this study is described on ICF Page No. 13 under the paragraph addressing compensation for injury resulting from the study and similarly also translated in the ICF Urdu version.	---
8	Application is for phase-II & Phase-III, it	Kindly provide the clinical trial approval for Phase II and	As per request to approve Phase-II &

	may be for phase-II only & after submission of Phase-II results then its Phase-III may be approved depending upon Phase-II results.	III trial together, as the nature of trial is competitive recruitment globally for both the phases of the trial. Once the Phase II will be completed, we will submit the preliminary data analysis and Independent (Study Monitoring Committee) SMC recommendation letter to start the phase III of the trial globally. In the other participating countries (UAE & Philippines) the clinical trial approval is granted for both Phase II and Phase III (Attached for reference). In order to achieve the recruitment timelines at the same time as in UAE and Philippines, we request you to kindle give the collective approval of Phase II and Phase III with the condition of submitting the recommendation letter from Independent SMC and preliminary data analysis of Phase II	Phase-III, please provide legal provisions from law of the land or from any stringent regulatory Authority.
9	It is informed in application that, test drugs IMPs will be imported, whereas comparator will be procured locally from NIH, Islamabad. Comparator procurement procedure & details regarding purchase of comparator from NIH need to be provided.	Response is same as explained in the Point No. 4 above	Please clarify that, NIH is manufacturer or importer of the comparator vaccine.
10	All proposed Clinical Trial Sites(s) are not approved for Phase-II studies/Clinical Trials.	Only (NIH) National Institute of Health Pakistan will participate in the Phase II of the trial and NIH had already applied for the clinical trial site license to DRAP on 23rd February 2022. Site inspection is awaited an	NIH, Islamabad is not approved CTS for Phase-II Clinical Trials.

		acknowledgement copy is attached for your reference.	
11	The composition of National Institute of Health's IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines. So, its IRB/ERC & NBC approval for the subject trial can't be considered. Institute is advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules, 2017, review the trial subsequently & issue a fresh approval. So both IRB/ERC & NBC approvals afresh need to be provided.	IRB composition of National Institute of Health (NIH) is as per ICH-GCP guidelines and bio-study rules 2017 i.e., it is composed of 5 members, one member (Imam Masjid) is non-scientific person and Dr. Najma is an independent member and has no affiliation with NIH, she is an employee of UKHSA. The list of IRB members and their notification is attached for your reference.	The composition of IRB is not as per ICH-GCP & the Bio-Study Rules, 2017.
12	GMP certificate of comparator's manufacturer (i.e. Beijing Institute of Biological Products Co. Ltd., China) need to be provided.	GMP certificate of Beijing Institute of Biological Products Co. Ltd is not available with NIH, as we are procuring the comparator locally from National Institute of Health (NIH). As Sinopharm is approved by DRAP, therefore EUA, COA and IB is attached.	GMP Certificate is a mandatory documents & need to be provided as per Rule 8 (2) & Form-II of the Bio-Study Rules, 2017.
13	CoPP/EUA of following need to be provided for; PIKA Recombinant COVID-19 Vaccine (CHO cell, S protein) Drug Substance, YS-SC2-010 Drug Substance. (COVID-19 Vaccine (Vero Cells) Inactivated)	a) CoA for investigational medicinal product is already submitted in the clinical trial application. EUA is not available as it is an investigational product right now. b) For comparator, CoA and EUA are attached.	As per reply none of the document provided. CoPP/EUA has been requested, which is a legal requirement.
14	It is informed that, Interim Analysis Report for Phase-I, PIKA Covid- 19 vaccine study is under preparation and will be submitted as part of the clinical trial	Interim analysis report for Phase I data was submitted to DRAP on August 26, 2022. An acknowledgement copy is attached for your reference.	Approval of the NBC, IRBs/ERC for Phase-II/III Clinical Trial is granted without reviewing the Phase-I Data.

	application dossier for the applied study once available. Details regarding Phase-I need to be provided.		
15	As per provided details regarding subject enrolment, it seems that sponsor is conducting Phase-II CT only in Pakistan, clarification needs to be provided that, why Phase-II will not be carried out at other two participating countries.	As the nature of trial is competitive recruitment globally, i.e. individual recruitment target for all the participating countries (Pakistan, UAE & Philippines) is not fixed. As soon as the total recruitment of 300 participants is achieved globally, phase II will be closed.	---
16	As IMPs are not registered, Emergency Use Authorization (EUA) Certificates for all IMPs need to be provided. Further lot/batch wise COAs of IMPs need to be provided, to be utilized in the trial after its approval.	Since the IP is the investigational product, therefore there is no EUA of IMP, whereas EUA for comparator is attached. Lot/batch wise COA of both IMP and Comparator is attached.	None of the claimed document is provided.
17	Sample label are provided but these are not as per ICH-GCP guidelines & as the study is double blinded so commercial labels or labels with IMPs name can't be used.	Study specific comparator label for Sinopharm is attached for your reference. As the comparator vaccine and the Investigational Product are different, therefore to make sure the blinding in this trial, there will be a dedicated un-blinding team to look after the IMP management and dispensing. Whereas the rest of the blinded staff will not have access to the IMP and will not be able to know that who receives the IMP and who is receiving the Comparator. By keeping two separate team at the site, blinding will be assured.	Double blinded Study so how & where it will be blinded. Further it is mentioned in form II that all All the quantities of the each of investigational product should be procured from one single source)

9. The DRK applicant has also submitted the reply in response to this office letter F.03-09/2022 DD (PS) dated 26th October 2022 and has attached following supporting documents.

i. Quotation slip for clinical trial liability insurance is attached.

ii. Material Transfer Agreement whereas **procedure/ SOP is required**.
iii. Vaccine supply agreement b/w Yisheng Biopharma (Singapore) Pte. Ltd and National Institute Health, Islamabad.
iv. Copy of EUA SARS-CoV-2 Vaccine (Vero cell), inactivated manufactured by M/s Beijing Institute of Biological Products China.
v. Trial (Phase II/III) Approval by FDA, Department of Health, Republic of the Philippines.
vi. Trial (Phase II/III) Approval by Ministry of Health & Prevention, UAE.

10. Dr. Syed Rooh Ul Arifeen Naqvi, Project Manager, DRK Solution, Lahore, has written a letter on behalf of Country Investigator (Prof. Dr. Aamer Ikram). He has stated that as per study protocol, the total recruitment in phase III is 9000 subjects. For Pakistan, the planned target recruitment in phase III is 3000 subject. As there are three countries i.e. UAE, Pakistan and Philippines, participating in Phase III of this clinical trial. There shall be a competitive recruitment among these participating countries. As soon as the global target i.e. 9000 for phase III is achieved, the countries will stop the recruitment. As phase II with targeted recruitment has been completed on October 10, 2022. Therefore, as per the study protocol, we requested for phase III clinical trial. The protocol states that SMC will also provide Go/No Go recommendation whether to proceed to phase III after reviewing safety data of all subjects enrolled in phase II until 07 days' post vaccination. Copy of SMC report status "Go Recommendation to proceed with the initiation of phase III study" with SMC charter for phase II results is attached in which SMC has given the recommendation to start the phase III of this clinical trial. As SMC has given the Go Recommendation for phase III, the participating countries (UAE and Philippines) are starting the phase III recruitment in the last week of the October 2022. Therefore, we request you to kindly give us favorable opinion to stat phase III so that we can catch up the other participating countries in time. Because if we do not recruit the participant in time the other countries will keep on recruiting and complete the recruitment target as the nature of the trial is competitive recruitment.

11. The SMC (Safety Monitoring Committee) is the Internal Yisheng Biopharma Committee formed to provide proactive, aggregate and holistic evaluation of safety profile of the investigational product (IP) over the developmental lifecycle of the product, with periodic and documented review of available safety data.

12. The SMC after evaluation and discussion of the presented safety data of phase 2 study 7 days post the booster dose of PIKA COVID 19 vaccine, has concluded that there are no safety signals noted 7 days' post vaccine administration. SMC wrote that period of 7 days is very short to provide a full safety assessment and therefore the safety evaluation must be a continuing activity.

13. The SMC provided the Go recommendation to proceed with the initiation of the phase 3 study. However, there are some precautions enumerated by the SMC chair to be observed and presented in the next SMC meeting on 27th October 2022.

- It was recommended by the SMC chairman that all the safety data should be presented with complete information on the vaccination date and AE start date for correlation.
- A more comprehensive data needs to be included for all unsolicited AEs;
    - Date when the symptoms started.
    - Date of vaccination.
    - Detailed list of all symptoms experienced by the subjects.
    - Methods or test performed to confirm the diagnosis.
- A clearer presentation and calculation of the number of solicited, local and systemic AEs and unsolicited AEs experienced by the subjects. Some signs and symptoms of reported unsolicited AEs may overlap with the solicited AEs being collected.

- To inform all investigators to be more cautious of any unsolicited AEs reported with reference to cardiac and gastric complaints, e.g. GERD, chest discomfort and an ECG must be performed to rule out any cardiac condition such as carditis or myocarditis.

14. In light of above following queries/ shortcomings were communicated vide this office F.No.03-09/2022 DD (PS) dated 03.11.2022.

i. Clarification/ relevant rule under which EPI/ Government supply can be sold to sponsor/ used for trial.

ii. The composition of IRB (on approval letter) of NIH is not as per ICH-GCP & Bio-Study Rules 2017 as only four members have been participated in the meeting in which subject trial was evaluated & approval granted. Further two members are not as per NIH IRB notification dated 26th November 2022.

iii. GMP certificate is required under rule 8(2) & Form-II of Bio-Study Rules 2017 and ICH-E6 (R2) (5.13.1) guidelines.

iv. SOP for masking/ blinding of locally purchased vaccine and where it will be blinded.

v. SOP for material transfer is required.

vi. Has SMC report been reviewed by NBC/IRBs? If yes, then their comments/ approval please.

vi. Reply from Dr. Syed Rooh Ul Arifeen Naqvi, Project Manager, DRK Solution, Lahore, in response to this office letter F.No.03-09/2022 DD (PS) dated 3rd November 2022 has been received. The reply has been evaluated in tabulated as under;

S. No.	**Shortcoming/ query**	**Reply**
1	Clarification/ relevant rule under which EPI/ Government supply can be sold to sponsor/ used for trial.	As NIH possess the EUA of comparator vaccine (Sinopharm), NIH is also arranging the comparator vaccine (Sinopharm). Once trial is approved by DRAP, NIH will arrange the vaccine for trial from Federal Directorate of Immunization and followed by re-packing, relabeling, storage and logistic of comparator vaccine. Ghazala Parveen has submitted that Federal directorate of Immunization is willing to provide the required doses of Sinopharm for research purposes.
2	The composition of IRB (on approval letter) of NIH is not as per ICH-GCP & Bio-Study Rules 2017 as only four members have been participated in the meeting in which subject trial was evaluated & approval granted. Further two members are not as per NIH IRB notification dated 26th November 2021.	NIH has notified the composition of IRB dated 1stOctober, 2022 with the signatures of Prof. Dr. Aamer Ikram, HI(M) and **he is the PI of the study. Also newly notified IRB has reviewed the SMC and after deliberation agreed with the recommendation of this report.**
3	GMP certificate is required under rule 8(2) & Form-II of Bio-Study	GMP certificate of M/s Liaoning Yisheng Biopharma co., Ltd issued by China Food and Drug administration is attached.

	Rules 2017 and ICH-E6 (R2) (5.13.1) guidelines.	**Certificate of GMP compliance of manufacturer for M/s Beijing Institute of Biological Products Co., Ltd issued by OGYEI National Institute of Pharmacy and Nutrition is attached.**
4	SOP for masking/ blinding of locally purchased vaccine and where it will be blinded.	SOP for blinding Procedure is attached.
5	SOP for material transfer is required.	Laboratory Manual and Lab Flow Chart of Q2 Solution is attached.
6	Has SMC report been reviewed by NBC/IRBs? If yes, then their comments/ approval please.	SMC report by IRBs of M/s CPTH, Al-Shifa Teaching Hospital and NIH has been reviewed and has given recommendation for recruitment of phase-III. NBC approval is also attached.

15. Secretary CSC presented the case before the Committee & representatives form CRO & Sponsor (Dr. Zenaida) also joined the meeting to answer queries raised by the CSC members. The Committee decided the case as follows:

Decision:

Dr. Zenaida on behalf of the Sponsor of the Study and representatives of CRO presented the case before CSC & replied the questions of the members of the Committee. After deliberation in the light of shortcomings observed and reply of Dr. Zenaida & representatives of the CRO, the Committee deferred the case and decided to give an opportunity to the applicant for responding to the following queries:

i. *The SMC report of Phase-II study is 07 days post the booster dose of PIKA Covid-19 Vaccine which is not sufficient regarding safety data & doesn't have interim analysis report/immunogenicity of Phase-II Clinical Trial.*
ii. *In report the SMC Chair, has shown concerns that, "all investigators to be more cautious of any un-solicited AEs reported with reference to cardiac & gastric complaints e.g. GERD, Chest Discomforts & an ECG must be performed to rule out any cardiac conditions such as carditis or myocarditis". Applicant was advised to explain that, what measures have been taken in this regard.*
iii. *The applicant could not justify the repacking, relabeling, storage & logistic of comparator vaccine.*
iv. *The blinding/masking procedure of IMPs, as presented by applicant was not satisfactory.*
v. *Applicant failed to provide GMP along with CoPP/Free Sale Certificate for comparator vaccine.*
vi. *Applicant failed to explain whether comparator vaccine being used in the trial is being studied with/ without permission of the manufacturer.*

2. The applicant informed that, there shall be competitive recruitment among participating countries. As soon as global target i.e. 9000 Subjects for the Phase-III is achieved, the countries will stop the recruitment. Keeping in view the competitive recruitment among the participating countries, the Committee decided that, an early meeting will be convened in-person or through Zoom, after receipt of reply to the queries/shortcomings.

AGENDA ITEM XXV:

APPROVAL & REGISTRATION OF CLINICAL TRIAL TITLED, "A PHASE-II, GLOBAL MULTI-CENTER, RANDOMIZED, DOUBLE BLIND, PARALLEL, -CONTROLLED, CLINICAL STUDY TO EVALUATE THE IMMUNOGENICITY & SAFETY OF DIFFERENT PRODUTION SCALE & BATCHES OF RECOMBINANT SARS-COV-2 FUSION PROTIEN VACCINE (V-01) IN ADULTS AGED 18-59 YEARS". (F. NO.03-05/2022 DD (PS).

Application is from Muhammad Tanseer Ali, CNIC No. 35401-6440356-9 of M/s Tigermed Consulting Pakistan, 7th Floor, Office No.712-713, High-Q Tower, Plot-1, Gulberg-5, Jail Road, Lahore wherein the applicant has requested for approval & registration of Clinical Trial titled, "*A Phase-I, Global Multi-Center, Randomized, Double Blind, Parallel, -Controlled, Clinical Study To Evaluate The Immunogenicity & Safety Of Different Production Scale & Batches Of Recombinant Sars-Cov-2 Fusion Protein Vaccine (V-01) In Adults Aged 18-59 Years*"**.** The application is on Form-II of the Bio-Study Rules 2017 along with prescribed fee of Rs.200000/- paid vide challan number 1574048628, dated 07th March 2022.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed processing fee	Fee of Rs.200000/- paid vide challan number 1574048628, dated 07th March 2022.
3	Investigator Brochure (s)	Attached
4	Final protocol	Attached.
5	Informed consent and participant information sheet (Urdu to English)	Attached.
6	List of participating countries	Pakistan only
7	Phase of trial.	Phase II * On protocol Phase-I is mentioned
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Only quantity provided complete details require to be submitted along with justification.
9	Site of the trial	i. Central Park Medical College & Hospital, Lahore. ii. Avicenna Medical College & Hospital, Lahore. iii. Indus Hospital & Health Network, Karachi. iv. Rehman Medical Institute, Peshawar Licenses of sites to act as Clinical trial site are not provided.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	i. Central Park Medical College & Hospital, Lahore. ii. Avicenna Medical College & Hospital, Lahore. iii. Rehman Medical Institute, Peshawar iv. Indus Hospital & Health Network, Karachi IRB approval is not attached.
11	Approval of National Bio-ethics Committee (NBC)	Not provided
12	CV's of the Investigators	CV of Dr. Muhammad Ahmad Dr. Waheed Ahmad, Dr. Fivzia Herekar, Dr. Javed Khan Attached. Site wise details of PI required.

13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not provided
14	Pre-clinical/clinical safety studies	Phase-II data published by Chinese Medical Journal provided
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	No Attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Total 1696 subjects will be recruited in Pakistan as informed by the applicant.
19	Name of Monitors & Clinical Research Associate	Tigermed Consulting Pakistan, Lahore. Mr. Muhammad Tanseer Ali Country Operation Manager, Faheem Shahzad, CRAs Team, Muhammad Salman Tariq, Abdullah Mir, Husnain Sajjad, Rimsha Shahid, Hasina Sarwar, Fatima Siddique.
20	Evidence of registration in country of origin.	Not attached
21	Copy of registration letter (if registered in Pakistan)	N/A
22	Sample of label of the investigational product / drug.	Provided.
22	Duration of trial	13 Months.
23	Undertaking on stamp paper.	Attached.

3. Accordingly, following shortcomings were communicated;
   i. Clarification regarding the Phase of trial.
   ii. IRB approval from Indus Hospital and Health Network, Karachi is required along with composition of committee i.e. names and designation of members.
   iii. Details of investigational drug / trial material to be imported along with Justification for Quantity of drug / trial material to be imported is required.
   iv. Approval of subject study from National Bio-ethics Committee (NBC) is not provided.
   v. COPP or GMP & Free sale Certificate and evidence of registration in the country of origin (if applicable) required.
   vi. Summary of Investigator Brochure is not provided.
   vii. Copy of licenses of sites to act as Clinical trial site are not provided.
   viii. CV's of the Investigators are provided however Site wise details of PIs are not provided.
   ix. Soft Copy of Final Protocol, Investigator Brochure, Pre-clinical data & Safety studies and Phase I & II trial data is required.

4. The reply to the observations as communicated to the applicant vide para 26/N and is as under: -

Shortcomings	Reply
Clarification regarding the Phase of trial.	The applicant has clarified that the trial is of Phase-II (1042-1045/Corr.)
IRB approval from Indus Hospital and Health Network, Karachi is required along with composition of committee i.e. names and designation of members.	The applicant has not provided the IRB approval of Indus Hospital and Health Network, Karachi only Composition of Committee is provided. (1046-1047/Corr.)
Details of investigational drug / trial material to be imported along with Justification for Quantity of drug / trial material to be imported is required	Name of product: - Recombinant SARS-Cov-2 Fusion Protein Vaccine (V-01) Total Number of Subjects: - 1696 IP Doses per Subject: -02 vials Total IP Doses: -3392 Backup Doses: -10%

	Total quantity of IP:-3732
Approval of subject study from National Bio-ethics Committee (NBC) is not provided.	Attached.
COPP or GMP & Free sale Certificate and evidence of registration in the country of origin (if applicable) required.	GMP certificate and DML attached.
Summary of Investigator Brochure is not provided.	Attached.
CV's of the Investigators are provided however Site wise details of PIs are not provided.	Attached.
Copy of licenses of sites to act as Clinical trial site are not provided.	Central Park Medical College and Hospital, Lahore, **applied.** Avicenna Medical College & Hospital, Lahore, **applied**. Rehman Medical Institute, Peshawar, **applied**. Indus Hospital and Health Network, Karachi (CTS-0047)

5. Accordingly, following shortcomings were communicated to applicant;

i) IRB approval for the trial/study under reference, from Indus Hospital and Health Network, Karachi, need to be submitted.
ii) Signed copy of notification of composition of IRB from Indus Hospital and Health Network, Karachi, should also be submitted.

6. Mr. Muhammad Tanseer Ali in response to this office letter issued has submitted the reply wherein he has attached the IRB approval for subject mentioned study along with composition of IRB for Indus Hospital Karachi.

A letter from Mr. Muhammad Tanseer Ali, Country Head & Sr. COM, Tigermed, Lahore, wherein he has stated that we hereby regret to inform you that Clinical Study "A Global, Multi-center, Randomized, Double-Blind, Parallel-Controlled Clinical Study to Evaluate the Immunogenicity and Safety of Different Production Scales and Batches of recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01) in Adults aged 18-59 Years" Protocol number: TG2108V01, will be terminated immediately due to global strategic considerations. We would like express our sincere gratitude to you for your great support to TG2108V01 in the past months.

7. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC considered the request of the applicant to withdraw the application, the same was confirmed by Muhammad Tanseer Ali, through Zoom link before the CSC. The Committee acceded to the request and rejected the case being withdrawn by the applicant.

AGENDA ITEM XXVI:

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.

Case is placed before CSC for their consideration.

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 un-blinding 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) **Note; Number of drug boxes sent to the site = 2117,2159,2185, 2202, 2214, 2231, 4020, 4154, 8102, 8142.** **Note; Study report can only be submitted after the end of the trial.**			

The request along with report is placed before CSC for consideration.

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.

vi. 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.

vii. Approval letter from "LSHTM Research Ethics Committee" of London School of Hygiene & Tropical Medicines. (Dated: 24th August, 2022)

viii. 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).

ix. Approvals from 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)

4.

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 Mohtarma 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, III, IV)	Approved (07-10-2022)	Attached

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 Military College, Rawalpindi, Koohi 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.

6. The Secretary presented the case before the Committee, Dr. Rizwana Chaudhry PI & Dr. Aasia Kiyani also joined the meeting in-person& the Committee decided the case as follows:

Decision:

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.

AGENDA ITEM XXVII:

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 Imatinib 600 Tablets Infliximab 160 vials
9	Site of the trial	Shaukat Khanum Memorial Cancer Hospital and research Center, Lahore. Pakistan Institute of Medical Sciences (PIMS) Islamabad. Shifa International Hospital, Islamabad. Agha Khan University Hospital AKUH, Karachi. 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. **Only the composition of IRB of SKCH&RC is attached.** **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. CoA & GMP certificate for Imatinib of Lec pharmaceutical, A Sandoz company, Poslovna is attached. CoA & GMP certificate for Infliximab of Jansen, Cilag AG, Switzerland is attached. **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. 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 as agenda item for CSC meeting to be held on 13.01.2022 (as its international trial in collaboration with WHO).

10. Submitted for consideration of CSC:

11. 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."

12 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.

13. 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

14. 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 deliberations decided to defer the case for further deliberation & due to paucity of time.

15. The Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

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.

AGENDA ITEM XXVIII:

ISSUANCE OF IMPORT LICENCE & CHANGE OF IMPs MANUFACTURER FOR SCYNEXIS PROTOCOL NUMBER SCY-078-305, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SCY 078 (IBREXAFUNGERP) IN PATIENTS WITH CANDIDIASIS INCLUDING CANDIDEMIA, CAUSED BY CANDIDA AURIS. (CARES)F. No.03-15/2019-DD (PS)

Application for issuance of import license & change of IMPs manufacturer for subject trial is from Dr. Sayed Faisal Mahmood (PI), Aga Khan University, Karachi, dated 19th November, 2022.

2. Applicant request is reproduced as under:

Respected Sir,
We have a drug import license for SCY-078 issued on June 16,2020, for a period of two years. Now we are requesting to renew the import license in order to continue the execution of this clinical trial.

Moreover. please be informed that, the manufacturer of the investigational product SCY'078-301 (Ibrexafungerp) Citrate 250 mg has been changed from Corealis Inc. pharma. Quebec, Canada to Syngene International Limited, Biocon Park. Unit-A1, Block FDC & Unit S18 FC 2nd Floor & S19, Plot No. 2, 3 & IV Phase, Bommasandra Industrial Area, Jigani Link Road. Bengaluru- 560099. India. However, the study drug will continue to be shipped from the sponsor site SCYNEXIS. Inc., 101, Hudson Street, suite 3610, Jersey City, NJ 07302, USA.

2. Applicant provided following documents:

i. Initial import license
ii. GMP Certificate of Syngene International Limited, India.
iii. Lot release certificate and
iv. Confirmation letter from the sponsor

3. *Details/summary of the trial is as follows:*

i. 15 subjects were approved, till date PI enrolled 04 subjects/patients out of 15 as per approved registration letter No. CT-0009.

DRAP Initial Approval	DRAP 1 Extension	DRAP 2 Extension	IP License
26th August 2020	15th October 2021	14th January 2022	16th June 2020 until 15th June 2022 (Two years)

Approved Quantity of IP	IP Received	IP Dispensed	IP Remaining
150 Bottles (4500 Tablets)	12 Bottles (360 tablets)	10 bottles (300 tablets)	2 bottles (60 tablets)

4. As per remaining enrolment 138 Bottles need to be imported. Packaging & dispatch by the Sponsor SCYNEXIS Inc. USA.

5. Submitted for constitution of panel of experts for inspection & consideration of CSC:

6. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and deliberation decided to approve the application for import of remaining quantity of IMPs- Ibrexafungerp "SCY-078" (02 bottles (60 Tablets)) manufactured by Syngene International Limited, Biocon Park. Unit-A1, Block FDC & Unit S18 FC 2nd Floor & S19, Plot No. 2, 3 & IV Phase, Bommasandra Industrial Area, Jigani Link Road. Bengaluru- 560099, which will be packaged & dispatched by the study sponsor M/s SCYNEXIS. Inc., 101, Hudson Street, suite 3610, Jersey City, NJ 07302, USA.

Further, applicant is directed to contact relevant field office for renewal of Import licence under the Drugs (Import & Export) Rules, 1976.

AGENDA ITEM XXIX:

ISSUANCE OF IMPORT LICENCE & CHANGE OF IMPs MANUFACTURER FOR SCYNEXIS PROTOCOL NUMBER SCY-078-305, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SCY-078-305 (IBREXAFUNGERP) IN PATIENTS WITH FUNGAL DISEASES THAT ARE REFRACTORY TO OR INTOLERANT OF STANDARD ANTIFUNGAL TREATMENT (FURI). F. No.03-61/2021-DD (PS)

Application for extension/renewal of subject Clinical Trial is from Dr. Saeed Hamid (PI) & Director, Clinical Trial Unit, Aga Khan University, Karachi, dated 10th August, 2022, received on 15th August, 2022.

2. Applicant request is reproduced as under:

Respected Sir,
Name of drug: Ibrexafungerp

We have a drug import license for SCY-078 issued on June 16,2020, for a period of two years. Now we are requesting to renew the import license in order to continue the execution of this clinical trial.

Moreover. please be informed that, the manufacturer of the investigational product SCY'078-301 (Ibrexafungerp) Citrate 250 mg has been changed from Corealis Inc. pharma. Quebec, Canada to Syngene International Limited, Biocon Park. Unit-A1, Block FDC & Unit S18 FC 2nd Floor & S19, Plot No. 2, 3 & IV Phase, Bommasandra Industrial Area, Jigani Link Road. Bengaluru- 560099. India. However, the study drug will continue to be shipped from the sponsor site SCYNEXIS. Inc., 101, Hudson Street, suite 3610, Jersey City, NJ 07302, USA.

2. Applicant provided following documents:

i. Initial import license
ii. GMP Certificate of Syngene International Limited, India.
iii. Lot release certificate and
iv. Confirmation letter from the sponsor

3. 15 subjects were approved, enrolled 11 patients out of 15 & 04 subjects remaining to be enrolled, as per approved license No. CT0027.

DRAP Initial Approval	DRAP 1 Extension	IP License
March 2021	14th January, 2022	05th May, 2021 until 04th May, 2023 (Two years)

Approved Quantity of IP	IP Received	IP Dispensed	IP Remaining
150 Bottles (4500 Tablets)	84 Bottles (2520 tablets)	62 bottles (1860 tablets)	22 bottles (660 tablets)

4. As per remaining enrolment 56 Bottles need to be imported. Packaging & dispatch by the Sponsor SCYNEXIS Inc. USA.

5. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion and deliberation decided to approve the application for import of remaining quantity of IMPs- Ibrexafungerp "SCY-078" (22 bottles (660 Tablets)) manufactured by Syngene International Limited, Biocon Park. Unit-A1, Block FDC & Unit S18 FC 2nd Floor & S19, Plot No. 2, 3 & IV Phase, Bommasandra Industrial Area, Jigani Link Road. Bengaluru- 560099, which will be packaged & dispatched by the study sponsor M/s SCYNEXIS. Inc., 101, Hudson Street, suite 3610, Jersey City, NJ 07302, USA.

Further, applicant is directed to contact relevant field office for renewal of Import licence under the Drugs (Import & Export) Rules, 1976.

AGENDA ITEM XXX:

APPLICATION FOR LICENSE TO ACT AS A GENERALIZED PHASE-III & IV CLINICAL TRIAL SITE AT M/S NATIONAL HOSPITAL & MEDICAL CENTER, LAHORE. F. No.15-15/2019-DD (PS)

Application was from Dr. Lt. Col (R) Dr. Usman Jilani Khan, 35201-1512148-7 Administrator National hospital and Medical Centre, Lahore, dated 9th February, 2022, along with fee of Rs. 100,000/-, deposited vide challan number 4620641082, dated 02-02-2022 to act as Clinical trial site for Phase III & IV clinical trials,

2. Summary of evaluation & details regarding attached documents are as follows:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached.
2	Prescribed processing fee	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).	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.	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.	Attached
8	Undertaking on affidavit	Attached

3. Accordingly, after initial scrutiny & fulfilment of necessary requirements, Chairman CSC / Director Pharmacy Services nominated following panel for inspection of subject Clinical Trial:

i. Dr. Masud Ur Rehman (The then Chairman CSC/Director Pharmacy Services)
ii. Dr. Nadeem Irfan Bukhari (The then CSC member/Dean College of Pharmacy, University of The Punjab)
iii. Prof. Dr. Javed Akram (The then CSC member/Ex-VC U.H.S. Lahore.)

4. Inspection panel conducted inspection on 09th March, 2022 & submitted the inspection report with following remarks:

Panel inspected the Hospital, keeping in view of ongoing trials at Hospital, technical staff present. The panel recommended the CTU of the Hospital for Phase –III and Phase-IV only.

- **Recommendation for approval**

5. However, the firm vide letter No. Nil, dated 04th September, 2022 requested for approval of the site for influenza study entitled Phase-III Randomized, Observer-Blind, Multi-Center Study, to evaluate the efficacy, immunogenicity & safety of Seqirus Cell based Quadrivalent Sub-Unit Influenza Virus Vaccine (QIVc) compared to Non-Influenza Vaccine when administered in healthy subjects aged 06 months through 47 months.

6. Secretary CSC presented the case before the Committee & the Committee decided the case as follows:

Decision:

The CSC after detailed discussion, in light of expert inspection panel recommendations and owing to trial specific request of the applicant dated 04th September, 2022 decided to defer the case for re-inspection. Further, the Committee delegated the power to the Chairman CSC for constitution of the inspection panel.
