DRAFT MINUTES OF THE 40TH MEETING OF THE CLINICAL STUDIES COMMITTEE HELD ON 17TH MARCH, 2023.

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The 40th meeting of Clinical Studies Committee was held on 17th March, 2023 in the committee room, Drug Regulatory Authority of Pakistan, G-9/4, Islamabad. The meeting was chaired by Dr. Obaidullah, Director Pharmacy Services. The meeting was started with recitation of the Holy Verses. Following members attended the meeting online through Zoom except Chairman and secretary.

1.	**Prof. Dr. Fazal Subhan**	Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar, Khyber Pakhtunkhwa.	Member
2.	**Prof. Dr. Saeed Ahmad Khan**	Professor of Medicine Bolan Medical College Quetta presently serving as head of medicine department Jhalawan medical college Khuzdar, Balochistan.	Member
3.	**Dr. Mirza Tasawer Baig**	Associate Professor in the Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi & Clinical Pharmacist at Dr. Ziauddin Hospital, Karachi, Sindh.	Member
4.	**Mr. Waqas Latif**	Data Analyst/Biostatistician in Quality Enhancement Cell (QEC) at University of Health Sciences, Lahore, Punjab.	Member
5.	**Mr. Ahsan Ul Haq Athar**	Deputy Director-II, Pharmacy Services Division-DRAP.	Secretary/Member

2. Mr. Nouman Yousuf, Hafiz Muhammad Jawad Ali, Malik Muhammad Asad (online on Zoom) and Shafqat Hussain Danish assisted the Committee and Secretary in presentation of the agenda.

AGENDA ITEM I:

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

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

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

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

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

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

ii. Study IMPs required along with justification:

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

iii. Quantity of IMPs required along with justification:

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

iv. Source of IMP:

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

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

vii. **Study design & details:**

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

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

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

Primary & Secondary Objectives

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

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

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

		This study is Phase I & III in multiple countries, only phase III part of study will be conducted and enrollment activities of phase III will be initiated when the safety data of phase-I will be released and analyzed.
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	***Only phase III part of this study will be conducted the enrollment amount of phase-III subjects will be maximum 2000 in Pakistan. The overall IMPs/ Placebo quantity plan to be imported sites in Pakistan is separate 3000 (with syringe), total 6000.***
9	Sites of the trial	National institute of Health, Islamabad 0-2000 global competitive enrolment.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref.No.4-87/COVID-134/NBC-23/ dated 07 February, 2023.
12	CV's of the Investigators	CV of Maj. Gen. Aamir Ikram is attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	***Not attached.*** ***Instead of GMP certificate issued by Government Authority, The GMP compliance issued by Firm is attached.***
14	Pre-clinical/clinical safety studies.	**Not Attached.**
15	Summary of Protocol	Attached
16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	0-2000 global competitive enrolment.
19	Name of Monitors & Clinical Research Associate	Abdullah Mir Muhammad Salman Tariq NIH, Islamabad.
20	Evidence of registration in country of origin.	**Not registered product.**
21	Copy of registration letter (if registered in Pakistan)	**Not applicable**

22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	Approximately 12 months
23	Undertaking on Stamp paper	**Not Attached.**

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

A. Investigator's Brochure (IB):

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

B. Protocol:

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

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

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

C. IRB/ERC & NBC

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

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

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

D. Other:

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

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

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

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

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

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

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

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

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

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

7. Investigator Brochure and Protocol has already been shared with CSC members.

Discussion:

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

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

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

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

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

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

Decision:

CSC after detailed discussion and deliberation decided to defer the Clinical Trial titled, "*A Randomized, Double-Blind Physiological Saline-Controlled Clinical Study to Evaluate the Efficacy,*

Safety and Immunogenicity of SARS-COV-2 Variant (BA.4/5) mRNA Vaccine (ABO1020) in Healthy Subjects 18 Years and Older Who Have Completed Full Vaccination" in the light of proposal of representative of M/s Abbogen regarding submission of revised protocol designed for Phase-II and Phase-III. Further, CSC decided to direct the applicant to submit following documents;

i. Safety and Efficacy data with Two doses along with Data Safety & Monitoring Committee (DSMC) report after completion of Phase-I studies.

ii. Valid DML issued by China NMPA/FDA.

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

8. The Decision of CSC of CSC was communicated to applicant vide this office letter F.No.16-39/2023 dated 03rd March 2023. Mst. Ghazala Parween, Chief BPD, NIH in response to this letter has submitted a letter ISB-BPD-ADMN-43 dated 9th March 2023 wherein she has enclosed;

i. Study progress report dated 1st March 2023
ii. Safety and Immunogenicity report dated 7th March 2023 (To evaluate the efficacy of ABO 1020against confirmed Covid-19 occurring from 14 days after the second dose, as compared to placebo (phase II/III-600 subjects)).
iii. safety and immunogenicity report, dated 16 Feb 2023 (to Evaluate the safety and tolerability of ABO 1020 within 28 days after each dose (Phase 1-30 subjects)).
iv. Independent Data Monitoring Committee (IDMC) reports

9. She has further submitted that globally subject recruitment is in progress and 13,300 subjects has been recruited. No safety issue has yet been reported/noticed. This is competitive recruitment and enrollment is near to complete. ln this scenario, it is submitted that CSC may kindly approve the subject study at earliest possible to participate in multi-country trial.

10. Following is the summary/ conclusion of progress reports as submitted by the Mst Ghazala Parween;

i. The safety report dated 14 December 2022 is that The safety data up to 7 days after vaccination in the phase I part showed no serious adverse event (SAE) or adverse events of special interests (AESI). All the reported adverse events were mild in severity. The adverse events were resolved within 2 days, without treatment or with the treatment of commonly used OTC drugs. Based on the available data, the sponsor considered the study vaccine (ABO1020) safe and well-tolerated. The adverse event after vaccination is manageable. The sponsor will continue to evaluate the safety profile of ABO1020 based on the cumulative safety data.
ii. Conclusion of the safety and Immunogenicity report dated 16th February 2023 is that the preliminary safety and immunogenicity results demonstrate that the study vaccine (ABO1020) is sale and well-tolerated, and induces a high humoral immune response against Omicron variant BA.5.
iii. Conclusion of the safety and Immunogenicity report dated 7th March 2023 is that the preliminary safety results demonstrate that the study vaccine (ABOl020) is safe and well-tolerated. ln general, the collected safety data up to l4 days after the 2 doses of vaccination showed ABOl020 is safe and well-tolerated, and the AEs are manageable. Firstly, no SAE, AESI were reported. Secondly, most reported AEs, both solicited and unsolicited, were mild or moderate in severity. Thirdly, the reported solicited TEAEs were transient, majority of the adverse events were resolved within 4 days, without treatment, or only managed with commonly used OTC drugs. The sponsor will continue to evaluate the safety profile of ABOl020 based on the cumulative safety data.

11. Following are the Independent Data Monitoring Committee recommendations as per submitted documents;

i. IDMC of this study has completed the review of study data in this stage, with data collected up to 14th December 2022 including phase I safety data report. 7 of 8 members

including chairman attended the meeting. In accordance with review of the safety data results IMDC has recommended that this study should be continuously executed and phase 3 part can be initiated per current protocol. (Phase 2/3 part in Indonesia can be initiated per Indonesia Protocol).

ii. IDMC of this study has completed the review of study data in this stage, with data collected up to March-8th-2023. 6 of 8 members including chairman attended this meeting. The following has been reviewed by the members.

l) Study Progress report, dated 0l March 2023

2) Safety and Immunogenicity report, dated 07 March 2023 [To Evaluate the efficacy of ABOl020 against confirmed COVID-19 occurring from l4 days after the second dose, as compared to placebo (Phase II/III- 600 subjects)]

3) Safety and Immunogenicity report, dated l6 Feb 2023 [To Evaluate the safety and tolerability of ABOl020 within 28 days after each dose (Phase I
- 30 Subjects)]

4) Protocol Version 2.0

In accordance with our review of the safety and immunogenicity data result, we hereby recommend that this study should be continuously executed, and the phase 3 trials continued per the current protocol. Phase 3 part in Pakistan can be initiated per Pakistan protocol.

Discussion

The case was deliberated in light of observations and response submitted by the applicant. The CSC also inquired that is it the ABO1020 (variant BA.4/5) vaccine for which the safety and immunogenicity report has been submitted applicant or otherwise. The CSC was appraised the that following reports have been submitted for ABO1020 (variant BA.4/5) vaccine.

i. Study progress report dated 1st March 2023
ii. Safety and Immunogenicity report dated 7th March 2023 (To evaluate the efficacy of ABO 1020 against confirmed Covid-19 occurring from 14 days after the second dose, as compared to placebo (phase II/III-600 subjects)).
iii. safety and immunogenicity report, dated 16 Feb 2023 (to Evaluate the safety and tolerability of ABO 1020 within 28 days after each dose (Phase 1-30 subjects)).
iv. Independent Data Monitoring Committee (IDMC) reports

Decision:

The CSC after detailed discussion and deliberation and considering Study Progress Report dated 01st March 2023, safety and immunogenicity report, dated 16th February, 2023 (to Evaluate the safety and tolerability of ABO 1020 within 28 days after each dose (Phase-I, 30 subjects)), Safety and Immunogenicity Report dated 07th March, 2023 (To evaluate the efficacy of ABO 1020 against confirmed Covid-19 occurring from 14 days after the second dose, as compared to placebo (Phase II/III-600 subjects)) and Independent Data Monitoring Committee (IDMC) reports submitted by the applicant decided to;

i. approve the phase III clinical trial titled as "A Randomized, Double-Blind Physiological Saline-Controlled Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of SARS-COV-2 Variant (BA.4/5) mRNA Vaccine (ABO1020) in Healthy Subjects 18 Years and Older Who Have Completed Full Vaccination".
ii. The overall IMPs/ Placebo quantity to be imported in Pakistan 6000 (including syringe).

AGENDA ITEM II:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED, "A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATE

THE EFFECT OF, Bi-26 (STAIN OF BIFIDOBACTERIUM LONGUM, B. INFANTIS) SUPLEMENTATION VS PLACEBO ON WEIGHT GAIN ON UNDER WEIGHT INFANTS", AL-SHIFA TRUST EYE HOSPITAL, RAWALPINDI. F. No.03-31/2023-DD (PS)

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

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

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

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

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

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

iv. Study IMPs required along with justification:

Intervention name	**Bi-26**	**Placebo**
Manufacturer	Danisco USA 3322-3329 Agriculture Drive, Madison, Wisconsin, 52716, USA.	Danisco USA 3322-3329 Agriculture Drive, Madison, Wisconsin, 52716, USA.
Specification	Each Sachet contains 1gm (I dose) 9 doses per carton	Each Sachet contains 1gm (I dose) 9 doses per carton
Main ingredients	*Bifidobacterium infantis (*Bi-26 stain*)*	Potato maltodextrin
Formulation	Sachet	Sachet
Appearance	White to light yellow powder	White to light yellow powder
Dose regimen and route of administration	First Day: Single dose sachet containing 1 gm /day for 28 days.	First Day: Single dose sachet containing 1 gm /day for 28 days.
Storage	Room Temperature (2-8°C)	Room temperature (2-8°C)
Batch number and expiration date	1104277614 17.10.2024	1104277612 11.10.2024

v. Quantity of IMPs required along with justification:

Study Intervention	**Test Drug**	**Placebo**
Intervention Name	Bi-26	Placebo
Dose Formulation	Powder	Powder
Each Sachet Contains	1 gm (single dose)	1 gm (single dose)

Quantity to be imported	10,890 sachet.
Total box to be imported	1220 cartons
Total subjects to be recruited in Pakistan	200 (226 including drop out)

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

vi. Number of subjects to be recruited: 396 Subjects (Globally)

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

viii. Study design & details:

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

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

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

Primary & Secondary Objectives

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

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

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached. **Printed on letter head of Al Shifa Trust.**
2	Prescribed Fee	Rs. 200,000/- deposited vide Slip number. 784900120783, dated 27th December, 2022.
3	Investigator Brochure (s) Investigator Brochure Addendum	Edition 3.0 Version 6 dated 31 March 2022 Addendum 1 version 2 31 May 2022
4	Final protocol	Attached Protocol: gates MRI-MNK01-301 Protocol Version 4.0 dated 12 September 2022.

5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Tanzania, Kenya, Bangladesh and Pakistan.
7	Phase of trial.	Phase – III
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Bi-26 + placebo = 1220cartons. Each carton contains 9 single dose sachet of Bi-26 or placebo Total subjects to be recruited in Pakistan =200 Subjects including drop out = 226 Sachet required for 226 subjects = 904 (2 sachets extra per week) Loss due to temperature excursion = 45 carton Loss at site = 45 carton Extra overage = 316 carton The required IMP for trial is 5600 doses Extra doses = 5530. **Firm needs to develop SOPs for logistic, established supply chain handling and storage of IMPs.**
9	Sites of the trial	Agha Khan University, Karachi The Central Park Teaching Hospital, Lahore. Shifa International Hospital, Islamabad. Avicenna Medical College and Hospital, Lahore Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi. Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad. Maroof International Hospital, Islamabad
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Agha Khan University, Karachi. The Central Park Teaching Hospital, Lahore (257-259). Shifa International Hospital, Islamabad (262-264). Avicenna Medical College and Hospital, Lahore (268-270) Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi (253-256). Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad (260-261) Maroof International Hospital, Islamabad (265-267)
11	Approval of National Bio-ethics Committee (NBC)	Not Attached.
12	CV's of the Investigators	CVs of following (site-PI & national-PI) are attached. Dr. Sonia Qureshi (Site-PI) at Agha Khan University, Karachi (178-204) Dr. Muhammad Fakhar Ul Zaman (Site-PI) The Central Park Teaching Hospital, Lahore (216-218). Dr. Munir Iqbal Malik (Site-Pi) Shifa International Hospital, Islamabad (209-215). Dr. Aneela Zareen (Site-Pi) Avicenna Medical College and Hospital, Lahore (222-227). Dr. Ume Sughra (National PI) Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi (235-249). Prof. Dr. Maqbool Hussain (Site-Pi) Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad (219-221).

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

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

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

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

Decision: -

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

Discussion;

Dr. Ume Sughra PI of the trial and Ms. Anum representative of IQVIA joined the meeting through Zoom and responded the queries of CSC as per following details:

a. As per investigator Brochure addendum there are no completed clinical studies with Bi-26 as of the time of this 1B addendum. Two ongoing studies with Bi-26 are described below. Then can we move for phase III trial?

PI of the trial replied that briefed the committee that this probiotic is already approved by the FDA since 2007 and probiotics that naturally occur in human body does not need safety studies and straight away we move to phase III studies. She informed that Bi-26 has been in commercial use since 2014 for inclusion in food and dietary supplement products globally, in North America, China, South Africa, Middle East, Europe, and Asia/Pacific countries. Based on the information provided by the manufacturer to the FDA, as well as other information available, the FDA had no questions regarding the manufacturer's conclusion that Bi-26 is GRAS under its intended conditions of use. But on query about product approval with intended use from any Regulatory Authority, the PI could not respond.

b. The PI also informed the committee that this trial has been started in Australia, New Zealand and Ghana and have not identified any adverse event and are considering it safe. The CSC emphasized that IQVIA has informed that Pakistan is first country where this trial will be initiated. The PI insisted that the study is undergoing in Ghana.

The SYNERGIE phase 2 study (Barratt 2022) evaluated different B. infantis strain EVC001 (claimed as genetically similar to Bi-26) but in instant case phase I & II studies have not been conducted with Bi-26

Decision:

The CSC after detailed discussion and deliberation decided to defer the Clinical Trial titled, "A PHASE III RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY EVALUATE THE EFFECT OF, BI-26 (STAIN OF BIFIDOBACTERIUM LONGUM, B. INFANTIS) SUPLEMENTATION VS PLACEBO ON WEIGHT GAIN ON UNDER WEIGHT INFANTS" for the following queries with relevant documents.

i. *As there are no completed clinical studies with Bi-26 as of the time of this 1B addendum and two studies with Bi-26 are ongoing. Is there any particular clinical/ safety study of Bifidobacterium Longum subspecies infantis strain Bi-26?*
ii. *The SYNERGIE phase 2 study (Barratt 2022) evaluated different B. infantis strain EVC001 (claimed as genetically similar to Bi-26) but in instant case Phase I & II studies have not been conducted with Bi-26 along with relevant guidelines from U.S. FDA or other regulatory authorities*
iii. *Kindly provide any evident document regarding approval of Bifidobacterium Longum subspecies infantis (Bi-26 strain) along with its intended uses from any Regulatory Authorities as claimed.*
iv. *Clarification regarding Bifidobacterium Longum subspecies infantis (Bi-26 strain) in Colony Forming Units (CFU) for already approved indications (if any) and current study.*
v. *Approval of subject clinical trial in Australia, New Zealand and Ghana as informed by the applicant during the meeting as not mentioned in application.*

AGENDA ITEM III:

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.

The following panel was constituted vide this office letter No. F. 15-02/2022-DD(PS) dated 22nd February 2023 for the inspection of CTU situated at M/s National Hospital & Medical Center, Lahore.

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

The National Hospital & Medical Center, Lahore, Licence has been expired and is under the process of renewal. The panel conducted the inspection on 24.02.2023 as per check list with following remarks.

"National Hospital & Medical Center is having all the required facilities. It is a tertiary healthcare health unit and registered with Healthcare Commission. The inpatient capacity is of 250 beds. The outpatient capacity is 1700 patients per day. Sufficient study staff exists. A system for reporting safety concerns and events is in place. Staff is trained in related matters. The panel recommends the unit for approval by the CSC as clinical Trial Site (CTS) for phase III & IV.

- **Recommended for approval.**

Decision:

The CSC in pursuance to the recommendations of the inspection panel and in the light of discussion/deliberations decided to grant the licence to M/s National Hospital and Medical Centre, Lahore to act as Clinical Trial Site for Phase- III and IV Generalized Clinical Trials only, under the Bio-Study Rules, 2017.

AGENDA ITEM IV:

APPLICATION FOR LICENSE TO ACT AS CTS FOR A RANDOMIZED, DOUBLE-BLIND CLINICAL STUDY OF THE EFFICACY AND SAFETY OF BCD-201 (JS BIOCAD) AND KEYTRUDA IN PATIENTS WITH

UNRESECTABLE OR METASTATIC MELANOMA FROM ONCOLOGY DEPARTMENT, ALLAMA IQBAL MEDICAL COLLEGE/ JINNAH HOSPITAL, LAHORE F. No.15-24/2023 DD (PS).

Application was received from Dr. Kausar Bano, CNIC No. 35201-1344676-4, Associate Professor, Head of Department of Oncology, Jinnah Hospital, Lahore, wherein she has applied to act as Clinical Trial Site for phase III for clinical trial/study tilted as "A Randomized, Double-Blind Clinical Study of the Efficacy and safety of BCD-201 (JS BIOCAD) and Keytruda in patients with Unresectable or Metastatic Melanoma". The application is on Form-I of the Bio-Study Rules 2017 with prescribed fee of Rs. 100,000/- submitted vide slip No.75048268589 dated 22nd December 2022.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	Rs. 100,000/- submitted vide slip No.75048268589 dated 22nd December 2022.
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	Public Sector Tertiary Care Hospital working under Government of the Punjab. Punjab Healthcare Commission **Regular License** attached that was valid up to 10th November 2022.
4	Details of premises including layout plan of the site.	Layout plan attached.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Department wise equipment list attached.
6	Names and qualifications of the above sections along with their staff.	Following staff list along with their CVs attached. Dr. Kausar Bano, Associate Professor, Dr. Fareeha Sheikh, Senior Registrar, Misbah Shahid, Pharmacist, Shama Amen, Nurse, Mohammad Abdullah, Research Coordinator.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	List of Allied Facilities, Waste Management Agreement and SOP for emergency handling attached.
8	Undertaking on stamp paper	Attached.

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

Study of the Efficacy and safety of BCD-201 (JS BIOCAD) and Keytruda in patients with Unresectable or Metastatic Melanoma".

4. It is proposed that trial specific inspection panel may be constituted as per practice or case may be placed before CSC. The panel at the time of inspection will verify the validity of license at the time of inspection to avoid further delay.

5. The case was placed before CSC in its 38th meeting held on 8th February 2023 and was decided as follows;

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

6. Accordingly, following panel was constituted vide this office letter No. F. 15-24/2023-DD(PS) dated 8th March 2023 for the inspection of CTU situated at Oncology Department of M/s Jinnah Hospital/ Allama Iqbal Medical College, Lahore.

d. Prof. Dr. Jaida Manzoor, Head of Department of Paeds Endocrinology, Children Hospital & Institute of Child Health (CH & ICH), Lahore.
e. Mr. Waqas Latif, Member CSC, University of Health Sciences, Lahore.
f. Mr. Abdul Rashid Sheikh, FID, DRAP, Lahore.
g. Mr. Ahsan-Ul-Haq Athar, Deputy Director (PS), DRAP, Islamabad **(coordinator).**

The Licence issued by Punjab Healthcare Commission has been expired on 10th November 2023 and is M/s Jinnah Hospital has submitted fee for re-registration dated 21.01.2023. The panel conducted the inspection on 24.02.2023 as per check list and has submitted the report with following remarks.

"The Jinnah Hospital, Allama Iqbal Medical College Lahore is a tertiary care hospital and has full-fledged, independent Oncology Department with more than 100 outdoor patients and 40 beds. A public sector organization with electricity back up with generators allied facilities and emergency working 24/7. Keeping in view the above, qualification, expertise & training of staff, the panel recommended the proposed CTS for approval for "A randomized, double-blind clinical study of the efficacy of BCD-201 (JS BIOCAD) and Keytruda in patients with Unresectable or Metastatic Melanoma".

- **Recommended for approval.**

Decision:

The CSC in pursuance to the recommendations of the inspection panel and in the light of discussion/deliberations decided to grant the licence to M/s The Jinnah Hospital, Allama Iqbal Medical College Lahore to act as Clinical Trial Site for a Phase- III Clinical Trial titled, "A randomized, double-blind clinical study of the efficacy of BCD-201 (JS BIOCAD) and Keytruda in patients with Unresectable or Metastatic Melanoma", under the Bio-Study Rules, 2017.

AGENDA ITEM V:

APPLICATION FOR LICENSE TO ACT AS CTS FOR A RANDOMIZED, DOUBLE-BLIND CLINICAL STUDY OF THE EFFICACY AND SAFETY OF

BCD-201 (JS BIOCAD) AND KEYTRUDA IN PATIENTS WITH UNRESECTABLE OR METASTATIC MELANOMA FROM ONCOLOGY DEPARTMENT, KING EDWARD MEDICAL UNIVERSITY/ MAYO HOSPITAL, LAHORE F. No.15-25/2023 DD (PS).

Application was received from Dr. Muhammad Abbas Khokhar, CNIC No. 35201-1344676-4, Associate Professor/ Head of Department of Medical Oncology and Radiotherapy, KEMU/ Mayo, Hospital Rd, Lahore, wherein he has applied to act as Clinical Trial Site for phase III for clinical trial/study tilted as "A Randomized, Double-Blind Clinical Study of the Efficacy and safety of BCD-201 (JS BIOCAD) and Keytruda in patients with Unresectable or Metastatic Melanoma". The application is on Form-I of the Bio-Study Rules 2017 with prescribed fee of Rs. 100,000/- submitted vide slip No.76812969 dated 22nd December 2022.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	Rs. 100,000/- submitted vide slip No.76812969 dated 22nd December 2022.
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	Public Sector Tertiary Care Hospital/ medical university working under Government of the Punjab. Punjab Healthcare Commission **Provisional License** dated 31st May 2012 and application for issuance of regular licence dated 18th December 2021 is attached.
4	Details of premises including layout plan of the site.	Layout plan attached.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Equipment list of Emergency unit, Oncology department, Radiology Therapy and Pathology department is attached.
6	Names and qualifications of the above sections along with their staff.	Following staff list along with their CVs attached. Dr. Muhammad Abbas Khokhar, Associate Professor Head of Department. Dr. Nadeem Zia**, Consultant Radiotherapist,** Dr. Sobia Yaqub, Pharmacist, Fauzia Nazir, Nurse, Lehrasip Ali, DEO/ Research Coordinator.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	List of Allied Facilities, Waste Management Agreement and SOP for emergency handling attached.
8	Undertaking on stamp paper	Attached.

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

Randomized, Double-Blind Clinical Study of the Efficacy and safety of BCD-201 (JS BIOCAD) and Keytruda in patients with Unresectable or Metastatic Melanoma".

4. The case was placed before CSC in its 38th meeting held on 08th February, 2023. The Committee decided the case as follows:

Decision: -

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

5. Accordingly, the following panel was constituted vide this office letter No. F. 15-23/2023-DD(PS) dated 8th March 2023 for the inspection of CTU situated at Oncology Department of M/s Jinnah Hospital/ Allama Iqbal Medical College, Lahore.

a. Prof. Dr. Jaida Manzoor, Head of Department of Paeds Endocrinology, Children Hospital & Institute of Child Health (CH & ICH), Lahore.
b. Mr. Waqas Latif, Member CSC, University of Health Sciences, Lahore.
c. Mr. Abdul Rashid Sheikh, FID, DRAP, Lahore.
d. Mr. Ahsan-Ul-Haq Athar, Deputy Director (PS), DRAP, Islamabad **(coordinator).**

6. The Provisional Licence dated 31st May 2012 issued by Punjab Healthcare Commission M/s Mayo Hospital has submitted inspection cost dated 18-12-2021 in favors of Healthcare Commission. The panel conducted the inspection on 24.02.2023 as per check list and has submitted report with following remarks.

"The Mayo Hospital working with King Edward Medical University (KEMU) Lahore is a tertiary care hospital. The Mayo Hospital Lahore is public sector Organization with full-fledged, independent Department of Medical Oncology & Radiology. The electricity back up provided with UPS and generators. Have allied facilities and emergency working 24/7. Keeping in view the above, qualification, expertise & training (trial related) of staff, the panel unanimously recommended the proposed CTS for approval for "A randomized, double-blind clinical study of the efficacy of BCD-201 (JS BIOCAD) and Keytruda in patients with Unresectable or Metastatic Melanoma".

- **Recommended for approval.**

Decision:

The CSC in pursuance to the recommendations of the inspection panel and in the light of discussion/deliberations decided to grant the licence to M/s The Mayo Hospital working with King Edward Medical University (KEMU) Lahore to act as Clinical Trial Site for a Phase- III Clinical Trial titled, "A randomized, double-blind clinical study of the efficacy of BCD-201 (JS BIOCAD) and Keytruda in patients with Unresectable or Metastatic Melanoma", under the Bio-Study Rules, 2017.

AGENDA ITEM VI:

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

Application was received from Mr. Muhammad Imran Naveed, CNIC:36501-5613013-7, Director, M/s Trials 360, 140 Al-hamara Town near PCSIR, Phase II, Lahore, Punjab, Pakistan, wherein the request has been made for license act as Clinical Research Organization (CRO). The application is on prescribed Form-I of the Bio-Study Rules 2017 along with a fee of Rs.300000/- submitted vide Slip number 79246300059, dated 4th January 2023.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed fee challan	Rs.300000/- submitted vide Slip number 79246300059, dated 4th January 2023.
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	SECP acknowledgment slips, Certificate of Incorporation, list of applied forms attached.
4	Details of premises including layout plan of the site.	Layout plan attached.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Not applicable as applied for CRO.
6	Names and qualifications of the above sections along with their staff.	The staff name and CVs attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Not applicable as applied for CRO.
8	Undertaking on affidavit	Attached

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

Name	Qualification	Division
Dr. Sanaullah Sajid	DVM (2011-2016) , M.Phil. (2016-2018) , PhD (2018-2022)	Clinical Operation & Medical writing
Dr. Samiullah Sajid	MBBS,China (2017-2023)	Medical advisor
Dr. Imran Naveed	Pharm D (2003-2008)	Regulatory Submission, training & Development
Miss Farwa Mehmood	BSc Biotechnology MS Biomedical Sciences	Clinical research Associate
Mr. Kamran Khan	Pharm. D (2015-2020)	Project Manager
Dr. Shaban Afzal	MBBS, China (2017-2023)	Data Manager
Mr. Hafiz Bilal Murtaza	BSc, MSc (statistics) M. Phil (Statistics) PhD Scholar	Bio-Statistician
Mrs. Aqsa Zaman	Pharm. D	Quality Assurance

Mr. Athar Aiman Khan	BSCS (2017-2021)	IT
Mr. SM Attiq Ur Rehman	B. Com (IT)	Admin & Finance
Mr. Ehsan Ul Haq	Applied Psychology	Admin & Finance
Mr. Hamza	Bachelor of Computer Science	Human Resource

4. In the light of above it has been observed that only two persons are working in the organization having the degree of MBBS from china and session mentioned is 2017- 2023. Hence it is proposed that panel may be constituted by the chairman CSC as per practice or case may be placed before CSC for its consideration. The may be requested to verify the expertise of the staff working in organization along with other requirements for CRO.

5. The case was placed before CSC in its 38th meeting held on 08th February, 2023. The Committee decided the case as follows:

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

6. Accordingly, the following panel was constituted vide this office letter No. F. 15-22/2023-DD(PS) dated 22nd February, 2023 for the inspection of proposed CRO M/s Trials 360 (SMC-PRIVATE) Limited, 140 Al-hamara Town near PCSIR, Phase-II, Lahore.

a. Prof. Dr. Nadeem Irfan Bukhari, College of Pharmacy, University of the Punjab, Lahore.
b. Mr. Waqas Latif, Member CSC, University of Health Sciences, Lahore.
c. Mr. Ahsan-Ul-Haq Athar, Deputy Director (PS), DRAP, Islamabad **(Coordinator).**

7. The panel conducted the inspection on 03.03.2023 as per check list and has submitted report with following remarks.

"Keeping in view the staff qualification, experience, IT facility, electricity backup, data security, archiving, SOPs and documents, personal training and collaboration with National and International Organizations, Panel unanimously decided to for approval to act as CRO.

- **Recommended for approval to act as CRO.**

Decision:

The CSC in pursuance to the recommendations of the inspection panel and in the light of discussion/deliberations decided to grant the licence to M/s Trials 360 (SMC) (Pvt.) Ltd, 140 Al-hamara Town near PCSIR, Phase II, Lahore, to act as Contract Research Organization, under the Bio-Study Rules, 2017.

AGENDA ITEM VII:

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

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

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

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

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

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

5. **Brief Summary:**

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

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

Sr.	Documents	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs. 200,000/- deposited vide slip number 799831064
3	Investigator Brochure (s)	Version 2.0, Dated: 4th August, 2022 is attached.
4	Final protocol	Attached ASPRE-AF Protocol v4.0 dated 29-10-2021
5	Informed consent and participant information sheet (Urdu to English)	Attached.
6	List of participating countries	Argentina Australia Brazil Canada Denmark India Italy Nepal Netherlands New Zealand Sweden Pakistan Spain UK
7	Phase of trial.	Phase – IV
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	**Test Drug:** Xarelto 20mg tablet To be purchased from Shifa Pharmacy
9	Site of the trial	**Site(s)** — **PI** **Shifa International Hospitals Ltd, Islamabad** — Dr. Saeed Ullah Shah
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached. IRB# 0135-22
11	Approval of National Bio-ethics Committee (NBC)	NBC approval reference letter No.4-87/NBC-813/22/110
12	CV's of the Investigators	CVs of following (PI) expert is attached.

		i. Dr. Saeed Ullah Shah, Consultant Cardiologist, Shifa International Hospitals Ltd Islamabad.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP certificate attached. CoPP attached.
14	Pre-clinical/clinical safety studies	Already marketed drug; so no pre-clinical, clinical and safety studies data is required.
15	Summary of Protocol	Attached in Protocol.
16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	36 Subjects in Pakistan (Competitive Recruitment)
19	Name of Monitors & Clinical Research Associate	Dr. Tehreem Zahid. CRA Dr. Sundus Dadan. CRA Dr. Palwasha Alavi. CRA Raja Waseem Akram. Research Pharmacist
20	Evidence of registration in country of origin.	Product is registered in Pakistan
21	Copy of registration letter (if registered in Pakistan)	Attached.
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	The duration of participation of each individual subject is **24 months** from the consent to last visit.
23	Undertaking on Stamp paper	Attached.

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

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

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

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

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

(6) Investigational products;

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

(7) Applicant details;

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

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

(8) Principal investigator(s):

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

(a) **Name:** Dr. Saeed Ullah Shah (**e) CNIC No.** CNIC 17301-4566737-3 (b) **Position:** Consultant Cardiologist. (c) **Institute:** Shifa International Hospital, Islamabad. (d) **Site(s):** i. Shifa Research Clinical Center, Shifa International Hospital, Islamabad. (CTS-0026)	
(9) No. of patients to be enrolled: 36 Subjects in Pakistan (Competitive Recruitment)	
(10) Maximum duration of trial or study: 24 Months	
(11) Further conditions, if any: Nil	
(12) Quantity of IMPs need to be imported: 20mg of one tablet for one patient/day (total patients=36) so 26,280 tablets of 20mg Xarelto will be purchased from local Shifa Pharmacy.	
(13) Sponsor: Population Health Research Institute Canada	
(14) Anticipated cost of the project: 460 CAD/Patient	

ii. IMPs required along with justification:

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

iii. Source of Investigational Medical Products (IMPs):

Pakistan

iv. Study design & details:

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

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

Site(s)	PI	Specialty	Phase of trial	Remarks

Shifa International Hospitals Ltd, Islamabad	Dr. Saeed Ullah Shah (National-PI)	Consultant Cardiologist	Phase-IV	---

Primary Objectives:

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

Secondary Objectives:

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

Decision:

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

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

8. Accordingly, CSC decision was communicated vide letter bearing number 16-38/2023-CSC dated 03rd March 2023.

9. Dr. Tehreem Zahid, Clinical research Associate on behalf of Applicant/PI Dr. Saeedullah Shah, submitted reply on 06th March 2023. Submitted reply is as under:

i. Details regarding the antidote of Rivaroxaban in case of any untoward event/ toxicity

Rivaroxaban is factor Xa inhibitor. Andexanet Alpha is a medicine that reverses the effects of Factor Xa Inhibitors, however, it is currently not available in Pakistan and it has not been approved by DRAP. As a result, in centers where these antidotes are not available, bleeding episodes will be managed via supportive treatment. Study medication will be discontinued and FFPS or packed red blood cells will be administered until the anticoagulation effect is weaned off.

ii. Purpose of the study is not elaborating advantages of the study regarding safety/efficacy.

NOACS are recommended as first-line treatment in non-operative atrial fibrillation. But no high-quality evidence is available to guide clinical practice in perioperative atrial fibrillation. This is critical as it is unclear whether the stroke mechanisms are the same in patients with perioperative AF compared to patients with non-operative AF. Moreover, while postoperative patients have an increased risk of bleeding, oral anticoagulation may help prevent other thrombotic events and thus confer additional benefits. Therefore, the benefit-risk balance of anticoagulation in this patient population is

unknown and requires further investigation. The current ASPIRE-AF trial will determine the efficacy and safety of oral anticoagulation in patients with perioperative AF after non-cardiac surgery which is yet to be standardized. The MANAGE trial however already demonstrates that high-risk patients can be safely anticoagulated in the early postoperative period and that oral anticoagulation may prevent thromboembolic events other than stroke in high-risk post-operative patients.

The key study objectives are to determine the effects of NOACS on the incidence of

a) A composite of life-threatening major and critical organ bleeding
b) Major bleeding according to ISTH
c) Hemorrhagic stroke

iii. Why control group has not been given any sort of intervention for comparison?

Clinical guidelines recommend oral anticoagulation for patients with non-operative AF and additional stroke risk factors, and most of them recommend NOACS as first-line therapy. But anticoagulation in perioperative AF is not standard of care and many physicians are not using oral anticoagulation in these patients. Published data from the POISE- I trial demonstrated that anticoagulation was not used in most patients with perioperative AF. In this trial across 190 centers in 23 countries,16.6% of patients with perioperative AF were prescribed oral anticoagulation at hospital discharge. Even in high-risk patients with a CHADS2 score of more than 3, only 20.9% were anticoagulated at discharge. More recent data from New Zealand demonstrated similar findings. Although the underlying reason for this is currently unclear, clinicians may assume that perioperative AF will not recur and is not associated with an increased stroke risk, and hence does not require anticoagulation. On the other hand, they may just be uncertain about the best option for their patients given the absence of RCTs evaluating the efficacy and safety of anticoagulation
in patients with perioperative AF. To establish the results no anticoagulation has not been given in control arm as this is already the current standard of care for perioperative AF.

iv. What are the advantages of the study over other anticoagulants available in the market e.g., heparin and warfarin etc?

Taken together, all four NOACs are well-studied, effective, and safe drugs with a low risk for medication interactions and no need for regular coagulation monitoring as compared to warfarin which has a lot of drug and food interactions and also required regular INR monitoring, so is for heparin which is not available in oral form and also required monitoring. These things make the NOACS ideal candidates for a clinical trial of oral anticoagulation in patients with perioperative AF. Any of the four drugs has no discernible advantage over their competitors. Compared to Vitamin K antagonists NOACs are easier to use, safer, and at least as effective.

Decision:

The CSC after detailed discussion including its observations and submitted responses decided as follows:

a. *to approve Phase-IV Clinical Trial titled, "Anticoagulation for Stroke Prevention in Patients with Recent Episodes of Perioperative Atrial Fibrillation After Non-Cardiac Surgery- The Aspire-AF Trial", to be conducted at following site:*

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

b. *to permit import of antidotes before start of study*

AGENDA ITEM VIII:

APPLICATION FOR APPROVAL OF ADDITIONAL IMPs AS PER AMENDED PROTOCOL VERSION 1.5 FOR ALREADY APPROVED CLINICAL TRIAL TITLED "TRANSNASAL CAPSULE

ENDOMICROSCOPY FOR VISUALIZATION OF THE SMALL INTESTINE IN ENVIRONMENTAL ENTERIC DYSFUNCTION (EED) POPULATION IN PAKISTAN. F. No.03-18/2020-DD (PS).

Application from Dr. Sayed Asad Ali, Professor, Department of Pediatrics & Child Health, Associate Dean, Research, Medical College, Aga Khan University, Karachi, dated 01st November 2021. Wherein request was for issuance of license for import of TNIT devices for Clinical Trial titled, "*Capsule Endomicroscopy for visualization of the small intestine in EED population in Pakistan study*", in reference to approved protocol version 1.5 of the trial.

S#	Device	Quantity required
1.	Trans Nasal Endomicroscopy Catheter	20
2.	Optical coherence tomography (OCT) imaging system	3
3.	Optical Probes	20
4.	Rotary Junctions	2
5.	Catheter Sheaths	15

2. It is submitted that, amendment application of subject trial was discussed in the 32nd CSC meeting & the Committee decided as under:

The CSC after deliberation / detailed discussion decided to approve the proposed amendments in the protocol Version 1.0 to Version 1.5 of already approved Clinical Trial titled, "Transnasal Capsule Endomicroscopy for Visualization of the Small Intestine in Environmental Enteric Dysfunction (EED) Population in Pakistan".

3. After evaluation following shortcomings observed & communicated:

i. Prescribed processing fee for miscellaneous application (i.e. Rs.25000/-) need to be provided.
ii. Justification regarding quantities of devices need to be clarified as per submitted protocol & subject recruitment status.

4. Reply from Prof. Dr. Sayed Asad Ali, Department of Pediatrics & Child Health, Associate Dean Research, Aga Khan University, Karachi, was received and applicant provided following prerequisites:

i. Prescribed processing fee for miscellaneous application (i.e. Rs.25000/-) paid vide challan no.730507107 dated 21st January 2022.
ii. Revised study protocol version 1.5 track change copy.
iii. Trans Nasal Endomicroscopy Compact Imaging System 1.1 (Instruction for Use).
iv. Trans Nasal Endomicroscopy Device Description 1.2
v. Trans Nasal Endomicroscopy (Instruction for use) Version 1.2
vi. Trans Nasal Endomicroscopy Compact Imaging System 1.1 (Description)
vii. Application regarding quantities of devices required as per submitted protocol & subject recruitment status.

5. Details of required equipment with accessories as per approved revised protocol is as follows:

The Trans Nasal Endomicroscopy Device details			
Item		Quantity	Remarks
i.	Research Imaging System and accessory tools	01	Mentioned in protocol page 07 of 14
ii.	Research Rotary Junction and accessory tools	01	Mentioned in protocol page 07 of 14
iii.	Imaging Probe (includes optical probe and introduction tube as one entity)	12	Mentioned in protocol page 10 of 14

iv.	Optical Probes	05	Mentioned in protocol page 10 of 14
v.	Introduction Tubes	03	Mentioned in protocol page 07 of 14

The Trans Nasal Endomicroscopy Device accessories details		
i.	Luer holders	05
ii.	Hemostatis with female/female Luer	05
iii.	Proximal Subsystems	20
iv.	pressure gauges	20
v.	Galinstan Bottles	10
vi.	60ml syringes	15
vii.	10ml syringes	30
viii.	5ml syringes	15
ix.	IR card	01
x.	Needles (for syringes, covered)	25
xi.	Female Luer caps	25
xii.	Markers	02
xiii.	Sterile Drapes	25

Decision: -

The CSC after detailed discussion and deliberation decided to approve the following additional quantities of IMPs / TNIT Devices along with accessories for Clinical Trial titled, "Capsule Endomicroscopy for visualization of the small intestine in EED population in Pakistan study", in reference to approved protocol version 1.5 of the trial:

S#	***Device***	***Quantity required***
i.	*Trans Nasal Endomicroscopy Catheter*	*20*
ii.	*Optical coherence tomography (OCT) imaging system*	*3*
iii.	*Optical Probes*	*20*
iv.	*Rotary Junctions*	*2*
v.	*Catheter Sheaths*	*15*

Required equipment with accessories as per approved revised protocol is as follows:

The Trans Nasal Endomicroscopy Device details			
Item		*Quantity*	*Remarks*
i.	*Research Imaging System and accessory tools*	*01*	*Mentioned in protocol page 07 of 14*
ii.	*Research Rotary Junction and accessory tools*	*01*	*Mentioned in protocol page 07 of 14*
iii.	*Imaging Probe (includes optical probe and introduction tube as one entity)*	*12*	*Mentioned in protocol page 10 of 14*
iv.	*Optical Probes*	*05*	*Mentioned in protocol page 10 of 14*
v.	*Introduction Tubes*	*03*	*Mentioned in protocol page 07 of 14*

The Trans Nasal Endomicroscopy Device accessories details		
i.	*Luer holders*	*05*
ii.	*Hemostatis with female/female Luer*	*05*
iii.	*Proximal Subsystems*	*20*
iv.	*pressure gauges*	*20*
v.	*Galinstan Bottles*	*10*
vi.	*60ml syringes*	*15*
vii.	*10ml syringes*	*30*
viii.	*5ml syringes*	*15*
ix.	*IR card*	*01*
x.	*Needles (for syringes, covered)*	*25*
xi.	*Female Luer caps*	*25*
xii.	*Markers*	*02*

xiii.	*Sterile Drapes*	*25*

AGENDA ITEM IX:

APPLICATION FOR CLOSE-OUT OF A PHASE-I CLINICAL TRIAL TITLED "AN OPEN-LABEL, PHASE-I CLINICAL STUDY TO DETERMINE THE SAFETY AND PRELIMINARY IMMUNOGENICITY OF SARS-COV-2 VARIANT MRNA VACCINE (LVRNA010) IN HEALTHY PARTICIPANTS AGED 18 YEARS AND OLDER", FORM CBSCR-ICCBS F. No.03-16/2022-CT (PS).

It is submitted that, subject trial was discussed in 38th Meeting of CSC

Decision:

The CSC after detailed discussion and deliberation decided as follows:

a. to approve the Phase-I Clinical Trial titled, "Open-Label, Phase I Clinical Study to Determine the Safety and Preliminary Immunogenicity of SARS-CoV-2 Variant MRNA Vaccine (LVRNA010) in Healthy Participants aged 18 Years and Older", under the Bio-Study Rules, 2017, to be conducted at International Center for Chemical & Biological Sciences, University of Karachi, Karachi. (CTS-0046).
b. Approval letter will be issued after inclusion of a clinician in the trial as Co-Principal Investigator
c. A total of 144 Subjects will be enrolled in the study & following mentioned quantities of IMP will be imported after getting necessary approval/NOC from concerned DRAP field office.:

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

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

2. Application received from Prof. Dr. Muhammad Raza Shah, General Manager, CBSCR, International Center for Chemical & Biological Sciences, University of Karachi, dated 02nd March, 2023.Wherein reply is in reference to registration letter (CT-0046) issued bearing even number, dated 22nd February, 2023.

3. Request of the PI/Applicant of Subject trial is reproduced as follows:

Subject: Closing the file of Phase-l clinical trial reference number 03-16/2022-CT (PS)

This is with reference to the trial entitled, "An Open-Label. Phase 1 Clinical Study to Determine the Safety and Preliminary Immunogenicity of SARS-CoV-2 Variant mRNA Vaccine

(LVRNA010) in Healthy Participants Aged 18 Years and Older". The subject trial was approved in 38th Clinical Study Committee meeting held on 08th February 2023.

Since the vaccine was designed for the protection against delta strain and the delta strain has completed its life cycle and washed out from the world so the sponsor decided to terminate the process of the trial and file for the aforementioned clinical trial should be closed in all regulatory bodies. It is requested that the file of the aforementioned trial may be closed.

I am really thankful to all staff members of DRAP and members of the CSC who put together a lot of efforts in reviewing and processing of the trial application. The approval letter received from DRAP of the clinical trial is enclosed to this application.

Decision:

The CSC acceded to the request of termination of Clinical Trial in Pakistan, titled, "An Open-Label, Phase-I Clinical Study to Determine the Safety and Preliminary Immunogenicity of SARS-CoV-2 Variant mRNA Vaccine (LVRNA010) in Healthy Participants aged 18 Years and Older", upon PI request and Sponsor decision.

AGENDA ITEM X:

CLOSE-OUT REPORT OF CLINICAL TRIAL TITLED "ANTI-CORONAVIRUS THERAPIES TO PREVENT PROGRESSION OF COVID-19. F. No.03-57/2021-DD (PS)

It is submitted that, subject application was approved in 27th CSC Meeting held on 24th June 2021. CSC decided the case as follows:

The CSC after detailed deliberation & discussion decided to grant approval for registration of the Phase-III clinical trial titled "Anti-Coronavirus Therapies to Prevent Progression of COVID-19".

2. Accordingly, Registration letter (CT-0031) was issued on 13th July, 2022 for a period of 12 Months (Copy attached) and with following quantities of IMPs:

S.No.	Investigational Drugs	Brand Names	Manufacturer	Quantity
01	Aspirin 75mg Tablets	---	M/s Medreich PLC, Warwick House, Plane Tree Crescent, Feltham, TW13 7HF, United Kingdom.	7280 Tablets
02	Colchicine 0.5 mg Tablets	---	M/s Tiofarma B.V., Benjamin Franklinstraat, Netherlands.	10740 Tablets
03	Rivaroxaban 2.5 mg Tablets	Xarelto	M/s Bayer AG, Leverkusen, Germany	5488 Tablets

3. Application was received from Dr. Khawar Kazmi, Visiting Faculty Department of Medicine, Professor & Consultant Cardiologist, Aga Khan University Hospital, Karachi, dated 12th December, 2022. Wherein FR is a **Close-Out Report** of the subject trial.

4. Details of Close-out report is as follows:

Total no. of Subject enrolled	55 (47 inpatients and 5 outpatients)
No. of Subjects Randomized	55 patients (47 inpatients and 5 outpatients) (Site wise breakup available in Appendix 1)
No. of Subjects dropped out	1 participant ID 75110001
No. of Subjects Withdrew Consents	1 participant ID 75110001

SIJSARs (if any)	None
SAE'S	26 SAEs (See attached report sorted by AEs ad then SAEs) (Appendix 2)
AE'S	4 AEs (Appendix 2)
PDs	1 minor protocol deviation for participant75220001 eGFR was in acceptable range but collected outside protocol defined window
Report of any previous submissions such as DRAP approval, Quarterly progress reports, SAE notification	Appendix 3 Reference No. F. No.03-57/2021-DD (PS)

5. Applicant attached following documents:

i. Site wise breakup
ii. SAEs & AEs Details
iii. Import Licence Copy
iv. Incineration details & approval from Sponsor

6. IMPs Inventory Record is as follows:

- UN-ASSIGNED UN-USED IP INVENTORY

IP NAME	Quantity AVAILABLE
RIVAROXABAN	53 Bottles
COLCHICINE	253 Boxes
ASPIRIN	200 Boxes

- ASSIGNED UN-USED AKU IP INVNTORY

INPATIENT	OUTPATIENT
Rivaroxaban= 5 bottles+ 96 Loose Tablets	Colchicine= 9 boxes
Colchicine= 12 boxes+ 20 Loose Tablet	Aspirin= 9 boxes
Aspirin= 5 boxes+ 47 Loose Tablets	--

- ASSIGNED UN-USED TABBA HEART IP INVEN TORY

IP Un-Used
Rivaroxaban= 10 bottles
Colchicine= 19 boxes + 28 Loose Tablets
Aspirin= 10 boxes

- ASSIGNED UN-USED JPMC IP INVENTORY

IP Un-Used
Rivaroxaban= 08 bottles
Colchicine= 30 boxes Tablets
Aspirin= 10 boxes

- IP Incineration:

Import license: 245012021DRAP (K) (Appendix 3)
Complete inventory of IP (imported, Used and unused)- listed below:

Drug	Total packs	Used	Unused
Rivaroxaban	98	22	76
Aspirin	260	26	234
Colchicine	358	48	310

7. In view of above, it is proposed that the matter may be placed before CSC for consideration & decision, please.

Decision:

The CSC decided that, the Chairman CSC constitute an expert panel for GCP-Compliance Inspection of the trial titled, "Anti-Coronavirus Therapies to Prevent Progression of COVID-19", reconciliation of IMPs as per DRAP approved quantities and process of incineration.

2. After destruction/incineration a complete GCP-Compliance, Drug Reconciliation & Destruction report will be submitted to the CSC for consideration.

3. IMPs Inventory Record is as follows:

- *UN-ASSIGNED UN-USED IP INVENTORY*

IP NAME	*Quantity available*
RIVAROXABAN	*53 Bottles*
COLCHICINE	*253 Boxes*
ASPIRIN	*200 Boxes*

- *ASSIGNED UN-USED AKU IP INVNTORY*

INPATIENT	*OUTPATIENT*
Rivaroxaban= 5 bottles+ 96 Loose Tablets	*Colchicine= 9 boxes*
Colchicine= 12 boxes+ 20 Loose Tablet	*Aspirin= 9 boxes*
Aspirin= 5 boxes+ 47 Loose Tablets	--

- *ASSIGNED UN-USED TABBA HEART IP INVEN TORY*

IP Un-Used
Rivaroxaban= 10 bottles
Colchicine= 19 boxes + 28 Loose Tablets
Aspirin= 10 boxes

- *ASSIGNED UN-USED JPMC IP INVENTORY*

IP Un-Used
Rivaroxaban= 08 bottles
Colchicine= 30 boxes Tablets
Aspirin= 10 boxes

- *Complete inventory of IP (imported, Used and unused)- listed below (for destruction/incineration):*

Drug	*Total packs*	*Used*	*Unused*
Rivaroxaban	*98*	*22*	*76*
Aspirin	*260*	*26*	*234*
Colchicine	*358*	*48*	*310*

AGENDA ITEM XI:

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 micro cellulose 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, 1976 and application for import of trial material.	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)
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. **ii.** Dr. Sidrah Nausheen (PI) (117-139/Corr.) **iii.** Dr. Sajid Sufi (Co-PI) (140-179/Corr.) **iv.** Dr. Shabina Ariff (Co-PI) (180-210/Corr.) **v.** 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. It is submitted that, the case was placed before CSC in its 36th Meeting held on 21st November, 2022 & the Committee decided the case as follows;

Decision:

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

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

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

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

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

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

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

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

Sr. No.	Descriptions / Shortcomings	Reply	Remarks
01	As per provided documents, composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval.	We have received a fresh ERC approval dated 25th November 2022 the updated ERC committee follows the bio study rules 2017 NDCP guidelines the fresh ERC approval is attached for your review.	---

02	As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.	Fresh ERC and NBC approval dated 05th December, 2022 are attached for your review.	---
03	AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials.	All the biological samples will be shipped to the sponsor which is the University of Sydney and there the analysis will take place and Material Transfer Agreement (MTA) for this purpose is in place and attached.	It is clarified that, blood samples of all 200 participants will be sent to designated laboratory for assay as mentioned in MTA.
04	GMP certificate of following manufacturer issued by respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided. 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	ii. **Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC,3207, Australia.** Pharmaceutical Packaging Professionals PTY Ltd (PPP) is a supporter of the Australian and international pharmaceutical, biotechnology and medical research sectors. It provides GMP of investigational product manufacturing, logical services distribute clinical supplies to Australia, New Zealand, Asia, North America and Europe. iii. **Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India** Esomeprazole RBX 40 mg is manufactured by Sun Pharma (manufacturer) - CoA is attached. iv. **Akesa pty Ltd., 6114l Flinders Lane, Melbourne VIC 3000 Australia** Akesa Pharma is a supplier who provided Esomeprazole from the manufacturer (Sun Pharma) - Akesa is an approved supplier and I have attached Akesa's ISO 9001 certificate license to sell, or supply is attached.	Provided all GMP certificate are not issued by the respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided as per the bio Study Rules, 2017.

05	Details regarding Subjects to be enrolled in Australia need to be provided.	• ESPRESSO received ethics approval on 07th Dec 2017 • First patient was enrolled on 01st April2019 • The current enrolment is 190 patients • The total sample size is 500 patients • One of the most significant challenges was COVID-19 which has significantly delayed recruitment and site activations	---
06	As per Informed Consent Form, the study is not insured & subjects need to file petition for compensation. It need to be clarified & study should be insured.	A revised consent form is attached the relevant section is highlighted for your review.	Attached consent form is not as per ICH-GCP guidelines & not safeguarding the rights of participants & there is nothing mentioned regarding Compensation/insurance for injuries or complications. Further, whenever ICF revised it should be provided in both English & local languages.
07	Financing & insurance details is not incorporated in trial protocol.	The relevant section of the protocol has been updated and attached for your review	Though relevant section in the trial protocol is revised but it is not informed in Pakistan what has been done for safety & insurance of participants. Further, it is informed that, previously Protocol No. CTC 0179 ESPRESSO, Version 2.0, dated 06th June, 2018 was attached & now revised protocol have Version 1.0 dated 18th October 2021. How it could be possible that, a [protocol is revised before it was directed to do so. Clarification in this regard needs to be provided.
08	Anticipated cost of the [project need to be informed.	A breakup of the cost is attached for your review. **(i.e.220,000 AUD)**	---

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

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

ii. Attached consent form is not as per ICH-GCP guidelines & not safeguarding the rights of participants & there is nothing mentioned regarding Compensation/insurance for injuries or complications.

iii. Further, whenever ICF revised it should be provided in both English & local languages.

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

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

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

Decision:

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

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

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

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

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

Sr. No.	Descriptions / Shortcomings	Reply	Remarks
01	*Provided all GMP certificate are not issued by the respective country drugs regulatory body need to be provided, further, connection & role*	GMP certificates and the role of manufacturers are attached. **(Page 465-479/Corr.)**	*Provided all GMP certificate are issued by manufacturer itself.*

	of mentioned manufacturers need to be provided as per the Bio Study Rules, 2017.		*GMP Certificate issued by respective country's drugs regulatory body need to be provided. Further, connection & role of mentioned manufacturers need to be provided as per the Bio Study Rules, 2017.*
02	*Attached consent form is not as per ICH-GCP guidelines & not safeguarding the rights of participants & there is nothing mentioned regarding Compensation/insurance for injuries or complications.*	AKU ERC approved consent form has been attached which is designed according to the Institutional guidelines. Section 6 of the consent form clearly addresses the compensation for injuries and complications. **(Page 480-499/Corr.)**	---
03	*Further, whenever ICF revised it should be provided in both English & local languages.*	Attached is the Urdu translation for the ICF, approved by AKU ERC.	---
04	*Though relevant section in the trial protocol is revised but it is not informed in Pakistan what has been done for safety & insurance of participants. Further, it is informed that, previously Protocol No. CTC 0179 ESPRESSO, Version 2.0, dated 06th June, 2018 was attached & now revised protocol have Version 1.0 dated 18th October 2021. How it could be possible that, a protocol is revised before it was directed to do so. Clarification in this regard needs to be provided.*	There are two separate types of protocols for the ESPRESSO study. One was sent by the University of Sydney (overall protocol) v2.0 dated 6th June 2018 and another one is Pakistan site protocol version 1.0 dated l0th Oct 2021 (approved by AKU ERC). Both protocols have been submitted to DRAP. Since the amendment regarding the insurance and indemnity was made in the Pakistan site protocol only; therefore, it was revised. Please refer to section 13.9 of the attached Pakistan site protocol regarding insurance. **(Page 500-526/Corr.)**	---

Decision:

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

i. *Provided all GMP certificate are not issued by the respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided as per the bio Study Rules, 2017.*
ii. *Proposed site for the trial is not approved for Phase-II Clinical Trials.*

AGENDA ITEM XII:

APPLICATION FOR CHANGE OF EXPERT STAFF ON CTS LICENCE NO-CT-0068 OF DOW UNIVERSITY OF HEALTH SCIENCES, OJHA CAMPUS, KARACHI. F. No.15-36/2021-DD (PS)

It is submitted that, application for approval of Clinical Trial Unit, Dow University of Health Sciences, Ojha Campus Karachi was placed before CSC in its 31st meeting held on 26th August 2021 & CSC decided as follows:

The CSC in pursuance to the recommendations of the inspection panel & in the light of discussion/deliberations unanimously decided to grant licence to following sites to act as generalized Clinical Trial Sites for Phase-I, II, II & IV Clinical Trials:

i. Clinical Trial Unit, Dow University of Health Sciences, Ojha Campus Karachi.
ii. Sindh Infectious Diseases Hospital & Research Center, NIPA, Gulshan e Iqbal, Karachi.

Further it is discussed that as there is no provision in the Bio-Study Rules 2017 to deal with the Phase-0 & preclinical studies and it is also not the mandate of CSC under the Bio-Study Rules 2017 to recommend or approve the site(s) for Phase-0 or preclinical studies. So, it was decided that, the matter regarding Phase-0/preclinical studies of M/s Dow Institute for Advanced Biological & Animal Research and Advanced Research Laboratory, DUHS, Ojha Campus Karachi be referred to the Authority for consideration/discussion & decision by the Authority.

2. Accordingly, Clinical Trial Site Licence No.0068 was issued on 10th September, 2023 for a period of three (03) years. (Which will expire on 09th September, 2026)

3. Application received from Dr. Izhar M. Hussain Executive Director, IBBPS-DUHS, Karachi on 17th November, 2023. Wherein F.R., it is informed that, Dr. Badar Faiyaz Zuberi has been retired from his services, and Dr. Sadia Asim has taken the charge of Director Clinical Trial site. Application is reproduced as under:

Request for the amendment in the Name Approved Expert Staff of Clinical Trial Site License No. CTS-0068

Respected Sir,

Reference to the subject, M/s Dow University of Health Sciences - Ojha Campus situated at KDA Scheme 33, Gulzar-e-Hijri, SUPARCO Road, Ojha Campus, Karachi, Pakistan, hereby request to amend the name of Approved Expert staff of Clinical Trial Site License No. CTS-0068 M/s. Dow University of Health Sciences - Ojha Campus. Please note that the approved expert staff of Clinical Trial Site License No. CTS-0068 Dr. Badar Faiyaz Zuberi has been retired from his services, and Dr. Sadia Asim has taken the charge of Director Clinical Trial site. Memorandum enclosed (Ref no: DUHS/Reg/2022/05-04-A) for reference.

Therefore, kindly consider the request to amend the name of Approved Expert Staff of Clinical Trial Site License No. CTS-0068 and issue the revised license. Look forward to your kind consideration & perusal of our request.

Thanks & Regards,

Dr. Izhar M. Hussain Executive Director

4. Applicant provided following documents;

i. Application on letter head.
ii. Fee Challan No. 841906534 of Rs. 25000/-
iii. Copy of Licence No. CTS-0068
iv. Memorandum regarding grant of Charge.
v. Letter regarding Non-Renewal of Contract.

Decision:

The CSC decided to approve the name of Dr. Sadia Asim as an Expert Staff for Clinical Trial Site, M/s Dow University of Health Sciences - Ojha Campus situated at KDA Scheme 33, Gulzar-e-Hijri, SUPARCO Road, Ojha Campus, Karachi (License No. CTS-0068)

AGENDA ITEM XIII:

APPLICATION FOR CHANGE OF EXPERT STAFF ON CTS LICENCE NO-CT-0069 OF SINDH INFECTIOUS DISEASE HOSPITAL & RESEARCH CENTER, NIPA, KARACHI. F. No.15-35/2021-DD (PS)

It is submitted that, application for approval of Clinical Trial Unit, Dow University of Health Sciences, Ojha Campus Karachi was placed before CSC in its 31st meeting held on 26th August 2021 & CSC decided as follows:

The CSC in pursuance to the recommendations of the inspection panel & in the light of discussion/deliberations unanimously decided to grant licence to following sites to act as generalized Clinical Trial Sites for Phase-I, II, II & IV Clinical Trials:

iii. Clinical Trial Unit, Dow University of Health Sciences, Ojha Campus Karachi.
iv. Sindh Infectious Diseases Hospital & Research Center, NIPA, Gulshan e Iqbal, Karachi.

Further it is discussed that as there is no provision in the Bio-Study Rules 2017 to deal with the Phase-0 & preclinical studies and it is also not the mandate of CSC under the Bio-Study Rules 2017 to recommend or approve the site(s) for Phase-0 or preclinical studies. So, it was decided that, the matter regarding Phase-0/preclinical studies of M/s Dow Institute for Advanced Biological & Animal Research and Advanced Research Laboratory, DUHS, Ojha Campus Karachi be referred to the Authority for consideration/discussion & decision by the Authority.

2. Accordingly, Clinical Trial Site Licence No.0069 was issued on 10th September, 2023 for a period of three (03) years. (Which will expire on 09th September, 2026)

3. Application received from Dr. Izhar M. Hussain Executive Director, IBBPS-DUHS, Karachi on 17th November, 2023. Wherein application it is informed that, Dr. Badar Faiyaz Zuberi has been retired from his services, and Dr. Sadia Asim has taken the charge of Director Clinical Trial site. Application is reproduced as under:

> *Request for the amendment in the Name Approved Expert Staff of Clinical Trial Site License No. CTS-0069*
>
> *Respected Sir,*
>
> Reference to the subject, M/s Sindh Infectious Disease Hospital & Research Centre, Karachi situated at NIPA, University Road, Karachi, Pakistan, hereby request to amend the name of Approved Expert staff of Clinical Trial Site, License No. CTS - 0069 M/s. Sindh Infectious Disease Hospital & Research Centre, Karachi.
> Please note that the approved expert staff of Clinical Trial Site License No. CTS-0069 Dr. Badar Faiyaz Zuberi has been retired from his services, and Dr. Sadia Asim has taken the charge of Director Clinical Trial site. Memorandum enclosed (Ref no: DUHS/Reg./2022/05-04-A) for reference.
> Therefore, kindly consider the request to amend the name of Approved Expert Staff of Clinical Trial Site License No. CTS - 0069 and issue the revised license. Look forward to your kind consideration & perusal of our request.
>
> *Thanks & Regards,*
>
> *Dr. Izhar M. Hussain Executive Director*

4. Applicant provided following documents;

i. Application on letter head.
ii. Fee Challan No. 18502180118 of Rs. 25000/-
iii. Copy of Licence No. CTS-0069
iv. Memorandum regarding grant of Charge.
v. Letter regarding Non-Renewal of Contract.

Decision:

The CSC decided to approve the name of Dr. Sadia Asim as an Expert Staff for Clinical Trial Site, M/s Sindh Infectious Disease Hospital & Research Centre, Karachi situated at NIPA, University Road, Karachi (License No. CTS-0069)

AGENDA ITEM XIV:

APPLICATION FOR APPROVAL ADDITIONAL QUANTITIES OF FOUR MEDICINES FOR CLINICAL TRIAL TITLED, "EVALUATING NEWLY APPROVED DRUGS IN COMBINATION REGIMENS FOR MULTI DRUG-RESISTANT TB WITH FLOUROQUINOLONE RESISTANCE (Q) (ENDTB-Q) PHASE-III CLINICAL TRIAL". F. No.03-17/2019-DD (PS)

Application was received from Dr. Naseem Salahuddin, Principal Investigator of endTB-Q Clinical Trial, The Indus Hospital & Health Network, Karachi, dated 24th February, 2023. Wherein FRs is a request for approval of additional quantities of four medicines for which importation is required till the end of the trial & therefore approval is requested from DRAP.

2. Application is reproduced as under:

With reference to our approved clinical trial endTB-Q (CT # 0006), and to the approval letter (F. No. 03-17/2019 DD (PS)) from DRAP dated 11 Feb 2020 for trial medicine quantities (enclosed), by way of submission of this application we are requesting permission for procurement and use of additional quantities of specific medicines for the approved endTB-Q trial.

The endTB-Q trial has had tremendous success in enrolling patients in Pakistan and is treating more patients with FQ-resistant MDR-TB than initially anticipated. As of 31-Dec-2022, the endTB-Q trial has enrolled 112 participants (also reported in Quarterly Progress Report for 4" quarter of 2022 submitted to DRAP on 13 Feb2023), and will continue enrolment until end of Mar2023. Concurrently, due to delays faced as a result of the COVID-19 pandemic, the trial completion has also been delayed and this has and may further result in some medicine quantities to expire without use. For these reasons, our importation requirement of clinical trial medicines has increased. The present request is made to ensure that all the patients enrolled in the trial receive adequate treatment.

In recent experience with procurement agencies, there have been supply chain issues that have surfaced especially during and after the pandemic. Our priority is to ensure an uninterrupted supply of medicines for MDR-TB treatment and well-being of the participants enrolled in the clinical trial. Thus, in view of all the factors described above, we hope through this application to prevent any treatment interruption which would be detrimental to the trial but most importantly for the patients.

The following documents are being submitted as a part of this application:

i. Copy of trial license for end TB-Q (CT # 0006)
ii. Copy of List of approved trial medicines (DRAP Approved, dated 11 Feb 2020, F. No. 03-17/2019 DD (PS))
iii. List of four medicines for which importation of additional quantities is required till the end of the trial, this letter to be considered as expedite approval.
iv. Consumption record and expiry details of four medicines mentioned above

Although the 'List of approved trial medicines (DRAP Approved, dated 11 Feb 2020, F. No. 03-17/2019 DD (PS))' includes a total of 45 medicines (16 IMPs and 29 ancillary meds), we are requesting for additional quantities of only four of the main IMPs that are used most frequently, which according to our latest forecasting are expected to come to shortage in the near future. We will continue to use the DRAP approval dated 11th February, 2020 F. No. 03-17/2019 DD (PS) as the main approval for importation of the medicines and quantities listed on it, alongside the additional quantities approval (i.e. as Addendum to F. No. 03-17/2019 DD (PS)) once granted by DRAP.

In light of the above, we request DRAP for an expedited approval of the requested additional quantities at the earliest to ensure that the trial is able to meet its objectives and provide uninterrupted treatment to our patients. We ensure our commitment to improving the health outcomes of MDR-TB patients and making zero compromises on patient safety.

We look forward to your positive response at the earliest.

Regards,

3. Applicant submitted following documents:

i. *Copy of trial license for end TB-Q (CT # 0006)*
ii. *Copy of List of approved trial medicines (DRAP Approved, dated 11 Feb 2020, F. No. 03-17/2019 DD (PS))*
iii. *List of four medicines for which importation of additional quantities is required till the end of the trial, this letter to be considered as expedite approval.*
iv. *Consumption record and expiry details of four medicines mentioned above*
v. *Fee of Rs. 25000/- in miscellaneous head paid vide challan number 19477402, dated 23rd February, 2023.*

4. Applicant requested following mentioned four medicine for which importation of additional quantities is required till the end of the trial:

S.No	Generic Name	Trade Name	Manufacturer	Country of Origin	Initially approved Qty.	Additional Qty. required
i.	Bdq (100) Bedaquline 100mg Film uncoated	SIRTURO 100mg Tablets	Recipharm/Janseen Pharma Service	India	42676	17296
ii.	Cfz(100) Clofazimine 100mg Capsule(s)	Lamprene capsule 100mg	Sandoz Private Ltd	India/France	47400	3800
iii.	Dlm(50mg) Delamanid 50mg Film coated tablet(s)	Deltyba 50mg	Otsuka Pharmaceuticals	Japan	145152	36288
iv.	Lnz(600) Linezolid 600mg Film coated tablet(s)	Linezolid Tablets 600me	Hetero labs United	India	30400	14400

5. Submitted for consideration of additional IMPs procurement request and constitution of an expert panel for reconciliation of used/expired drugs, please.

Decision: -

The CSC decided to approve the following additional quantities of IMPs for Clinical Trial titled, "Evaluating Newly Approved Drugs in Combination Regimens for Multi Drug-Resistant TB with Fluoroquinolone Resistance (Q) (endTB-Q) Phase-III Clinical Trial", (CT-0006), to ensure that, the trial able to meet its objectives and provision of uninterrupted treatment to trial participants:

S.No	Generic Name	Trade Name	Manufacturer	Country of Origin	Initially approved Qty.	Additional Qty. required
i.	Bdq (100) Bedaquline 100mg Film uncoated	SIRTURO 100mg Tablets	Recipharm/Janseen Pharma Service	India	42676	17296

ii.	Cfz(100) Clofazimine 100mg Capsule(s)	Lamprene capsule 100mg	Sandoz Private Ltd	India/France	47400	3800
iii.	Dlm(50mg) Delamanid 50mg Film coated tablet(s)	Deltyba 50mg	Otsuka Pharmaceuticals	Japan	145152	36288
iv.	Lnz(600) Linezolid 600mg Film coated tablet(s)	Linezolid Tablets 600me	Hetero labs United	India	30400	14400

2. Further, it is also decided that, the Chairman CSC will constitute an expert panel for GCP-Compliance Inspection of the trial and for reconciliation of IMPs as per DRAP approved IMP quantities. The expert panel's GCP-Compliance & IMPs reconciliation report will be submitted to the CSC for consideration and further decision.

AGENDA ITEM XV:

REQUEST FOR APPROVAL TO IMPORT STUDY MEDICINES FOR RESEARCH PROJECT TITLED AS "AZITHROMYCIN & CEFEXIME TREATMENT OF TYPHOID IN SOUTH ASIA TRIAL (ACT-SOUTH ASIA TRIAL). F.NO.03-51/2020 DD (PS).

Application was received from Prof. Dr. Farah Naz Qamar, Associate Professor, Department of Pediatrics & Child Health, Aga Khan University Hospital, Karachi, received on 24th January 2022 & 13th March, 2023. Wherein application is a request for protocol amendment, submitted with a prescribed fee of Rs.25000/- deposited vide challan no.481865936584, dated 20th January 2022. PI also provided trial progress report.

2. Progress report for subject cited clinical Trial (Registration No: CT-0030) is submitted as follows:

I. Background

Typhoid and paratyphoid (enteric)fever affects more than 11 million children and adults globally each year including 7 million in South Asia. Up to 1% of patients who get typhoid may die of the disease and, those who survive, a prolonged period of ill health and catastrophic financial cost to the family may follow. ln the last 20 years, treatment of typhoid fever with a7-day course of a single oral antimicrobial, such as ciprofloxacin, cefixime or azithromycin, given in an out-patient setting has led to patient recovery in 4 to 6 days without the need for expensive hospitalization. Increasing antimicrobial resistance in Asia and sub-Saharan Africa, threatens the effectiveness of these treatments and increases the risk of prolonged illness and severe disease. The recent emergence of a particularly resistant typhoid strain in Pakistan, and subsequent international spread, adds urgency to this problem and Salmonellas now listed as a high (Priority 2) pathogen by World Health Organization (WHO).

II. Study procedures

a. Methodology:

Design	***A randomized (1:1), participant- and observer-blind , multi-center Phase-IV trial***
Sample size	*560 suspected and confirmed case of typhoid fever* **** Initially 375 subjects approved for the trial, application for an increase in the trial subject recruitment is under process***
Study population	*Patients aged ≥ 2 years (and ≥ 10kg)to 65 years old with suspected uncomplicated typhoid fever.*
Study sites	*The Aga Khan University Hospital* *. The Aga Khan Hospital for Women Karimabad* *. The Aga Khan Hospital for Women Garden*

	. National Institute of Child Health (NICH)
Study treatments	*Arm A: Azithromycin 2Omg/kg/day oral dose once daily (maximum 1gm/day) AND Cefixime 20-30mg/kg/day oral dose in two divided doses (maximum 400mg bd) for 7 days.* *Arm B: Azithromycin 2Omg/kg/day oral dose once daily (Max 1gm/day) for 7 days AND Cefixime-matched placebo for 7 days.*
Study duration	*36 months*

b. Biological sample collection:

Number of tests are performed at screening and enrollment. For screening five rapid diagnostic tests are performed including COVID-19 antigen, C-reactive protein (CRP), malaria, dengue, and scrub typhus. Once the patient is eligible for enrollment blood culture, complete blood count, liver and kidney function tests are performed. ln addition, stool and urine samples, and COVID-19 PCR is collected.

c. Follow up visits:

The patients are routinely followed up via telephone or face-to face contact twice a day for the first seven days of antimicrobial treatment (and longer if the symptoms have not resolved). Caregivers are instructed to be consistent and measure temperature always at the same location (oral or axillary) for each patient and approximately at the same time. Face to face follow up by participant attendance at the clinic at day7, L4,28and90if patients had positive blood or stool culture for S. Typhior S. Paratyphi at the time of enrollment.

III. Study Progress since DRAP Approval - 13 July 2021

As soon as the final approval from DRAP was received, study related activities were started. The details are as follows:

a. Importation of study drug:

As the first step, we took import license from Karachi DRAP office for the import of study drugs from Nepal. The allotted drugs were procured successfully from Nepal in two shipments to kick start study. The quantity procured as per approval is summarized in table below:

S.No.	***Name of drug***	***Total approved quantity of medicines***	***Quantity in first shipment***	***Quantity in second shipment***
1	*Azithromycin 250mg*	*200 Strips*	*60 strips*	*140 strips*
2	*Azithromycin 500mg*	*416 Strips*	*134 strips*	*282 strips*
3	*Azithromycin Suspension 15ml.*	*100 Bottles*	*40 bottles*	*60 bottles*
4	*Azithromycin Suspension 30ml.*	*600 Bottles*	*40 bottles*	*560 bottles*
5	*Cefixime 100 mg DT*	*2300 Strips*	*25 Strips*	*1600 strips*
6	*Cefixime 400 mg*	*668 Strips.*	*30 Strips*	*638 strips*

b. Project take off meeting and Interdepartmental collaborative meetings:

A formal Project take off meeting was arranged with in the department. This meeting was attended by study investigators, study coordinator and frontline people from finance, admin, HR, transport, and Infectious Diseases Research Lab (IDRL) staff. Site specific meetings were also conducted at the AKUH, and other study sites attended by site administrators, nursing supervisors, site obstetricians and other relevant staff. ln these meetings, study procedures were explained in detail and expected issues were discussed.

c. Training of study staff:

Study team including research associates, senior research assistants, data collectors, phlebotomist were hired in due time. A two-day extensive training was conducted by the study investigators and coordinator; in which the following important points were covered:

- *Study protocol and objectives*
- *Detailed orientation on study procedures and methodology*
- *Recruitment process*
- *Consenting*
- *Study tools and forms*
- *Handling and storage of study drugs*
- *Drug dispensing*

- *Drug adverse event identification*
- *Performance of rapid diagnostic tests*
- *Biological sample collection and transport*
- *Cold chain maintenance*
- *Tagging and labelling (sample bottles and patient record files)*
- *Maintaining logs and records*
- *Randomization on Clires application*
- *Data entry in Clires application*
- *Visit of study site and feasibility check*

d. Site specific arrangements of logistics

Arrangement of logistics including a desktop and phone set, office space, stationary, forms for data collection, office supplies, kits for biological sample collection, ice packs, cool box and labels etc. were arranged in due time.

e. Initiation of enrolments:

The enrolment is soon to start in a step wise manner. The study team is planning to start the enrolment form NICH from end of December 2027 and extend to other sites. It is anticipated that all the sites will be functional by the end of January 2022.

IV. <u>Way Forward</u>

- *Initiation of enrolment on all sites by end of January 2022.*
- *Achievement of study sample size in stipulated study time frame.*
- *Follow up of enrolled patients to assess their compliance, feedback and any adverse effect experienced by them.*
- *Record and notify any adverse/serious adverse event.*
- *Submission of progress reports on timely basis.*

3. Justification for amendment in trial protocol version from **1.3** to **1.4** due to an increase in trial sample size (i.e. **375** Subjects to **560** Subjects) & additional requirement of IMPs is as follows:

Justification by PI:

With this letter we would like to request an amendment in patient sample size and quantity of drugs on ACT South Asia Trial (CT-0030). According to initial approval, 375 patients will be enrolled in the study however, keeping in view the possible exclusions due to COVID-19 and patients lost-to-follow up we have increased the sample size to 560 patients. To cater the increase in patient sample size we would like to increase the quantity of medicines and number of shipments. The revised quantity of medicines will be procured in six shipments during the entire period of study. The duration and all other study procedures will remain the same. The revised quantity of medicines mentioned in table below will be procured in six shipments during the entire period of study:

S.No.	***Name of drug***	***Total approved quantity of medicines***	**Revised Quantity of IMPs**	***Quantity in first shipment***	***Quantity in second shipment***	**Remaining quantity to be shipped in next six shipments**
1	*Azithromycin 250mg*	*200 Strips*	*909 Strips*	*60 Strips*	*140 Strips*	***709 Strips***
2	*Azithromycin 500mg*	*416 Strips*	*2178 Strips*	*134 Strips*	*282 Strips*	***1762Strips***
3	*Azithromycin Suspension 15ml.*	*100 Bottles*	*280 Bottles*	*40 Bottles*	*60 Bottles*	***180 Bottles***
4	*Azithromycin Suspension 30ml.*	*600 Bottles*	*1200 Bottles*	*40 Bottles*	*560 Bottles*	***600 Bottles***
5	*Cefixime 100 mg DT*	*2300 Strips*	*2400 Bottles*	*25 Strips*	*1600 Strips*	***775 Strips***
6	*Cefixime 400 mg*	*668 Strips.*	*1200 Strips*	*30 Strips*	*638 Strips*	***532 Strips***

4. Applicant/PI provided following requisite documents:

i. NBC approval letter reference number Ref:4-87/NBC-492/21/916 dated 15th December 2021, for increase in trial sample size amendment.

ii. Aga Khan University Hospital, IRB approval for protocol amendment from version 1.3 to 1.4 dated 21st December 2021, due to trial sample size amendment.
iii. Prescribed processing fee of Rs.25000/- deposited vide challan no.481865936584, dated 20th January 2022.

5. It is submitted that, due to delay in CSC notification the application could not be processed timely. Meanwhile, both NBC & AKUH-IRB approvals are expired also. In the case, it may be advised to PI to submit NBC & IRB approval & case may be discussed subject to provision of latest NBC & IRB approvals.

6. Trial progress report & application for amendment in already approved Clinical Trial titled "*Azithromycin & Cefixime Treatment of Typhoid in South Asia Trial (ACT-South Asia Trial)*" from version 1.3 to 1.4 due to an increase in trial sample size (i.e. **375** Subjects to **560** Subjects) & additional requirement of IMPs as described by the PI are placed for consideration of CSC, please.

Decision: -

*The CSC after detailed discussion and deliberation decided to approve the amendment in protocol version 1.3 to 1.4 of already approved Clinical Trial titled "Azithromycin & Cefixime Treatment of Typhoid in South Asia Trial (ACT-South Asia Trial)", and an increase in trial sample size (i.e. **375** Subjects to **560** Subjects) along with following additional IMPs required due to increase in sample size:*

S.No.	***Name of drug***	***Total approved quantity of medicines***	***Quantity in first shipment***	***Quantity in second shipment***
i.	*Azithromycin 250mg*	*200 Strips*	*60 strips*	*140 strips*
ii.	*Azithromycin 500mg*	*416 Strips*	*134 strips*	*282 strips*
iii.	*Azithromycin Suspension 15ml.*	*100 Bottles*	*40 bottles*	*60 bottles*
iv.	*Azithromycin Suspension 30ml.*	*600 Bottles*	*40 bottles*	*560 bottles*
v.	*Cefixime 100 mg DT*	*2300 Strips*	*25 Strips*	*1600 strips*
vi.	*Cefixime 400 mg*	*668 Strips.*	*30 Strips*	*638 strips*

2. Further, it is also decided that, the Chairman CSC constitute an expert panel for GCP-Compliance Inspection of the trial and for reconciliation of IMPs as per previously approved IMP quantities. The expert panel's GCP-Compliance & IMPs reconciliation report will be submitted to the CSC for consideration and further decision.

AGENDA ITEM XVI:

APPLICATION FOR AMENDMENT IN ICF OF CLINICAL TRIAL TITLED, "A RANDOMIZED, DOUBLE-BLIND CLINICAL STUDY OF THE EFFICAY AND SAFETY OF BCD-201 (JS BIOCAD) AND KEYTRUDA IN PATIENTS WITH UNRESECTABLE OR METASTATIC MELANOMA" F. No.03-24/2023-CT

The case is an application vide letter No. Nil dated 09-03-2023 (Fee Challan Slip Number 454289381 for Rs. 25000/=) from Dr. Syed Rooh Ul Arifeen Naqvi, Project Manager, DRK Pharma Solutions (Pvt.) Ltd. Lahore (Contract Research Organization) wherein he has notified about change of Insurance Company in Section 20 of Informed Consent Form (ICF) (PK & Non-PK) for already approved clinical trial titled as A RANDOMIZED, DOUBLE-BLIND CLINICAL STUDY OF THE EFFICAY AND SAFETY OF BCD-201 (JS BIOCAD) AND KEYTRUDA IN PATIENTS WITH UNRESECTABLE OR METASTATIC MELANOMA

2. **IGI** Insurance company was tentatively mentioned previously. Now, **CHUBB** insurance company will provide the participant insurance for this trial. Version number of ICF will remain same.

3. The applicant has informed that change of insurance company in ICF is also being notified to respective site IRBs and NBC. Updated ICF has also been submitted.

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

Site(s)	**PI**	**Specialty**	**Phase of trial**
Shifa International Hospitals Ltd, Islamabad	Dr. Saud Ghazi (National-PI)	Oncologist	Phase- III
Shaheed Zulfiqar Ali Medical University, Islamabad.	Dr. Qasim M Buttar, Site-PI	Oncologist	Phase-III
Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.	Dr. Samir Fasih, Site PI	Oncologist	Phase-III

5. The intimation for endorsement/approval/notification for change of Insurance Company in Informed Consent Form is placed before Clinical Studies Committee.

Decision: -

The CSC after detailed discussion and deliberation acceded the request and approved the amended/revised Informed Consent Form of already approved Clinical Trial titled "A Randomized, Double-Blind Clinical Study of the Efficacy and Safety of BCD-201 (JS BIOCAD) and Keytruda in Patients with Unresectable or Metastatic Melanoma"

AGENDA ITEM XVII:

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

It is submitted that, subject application was placed before CSC in its 38th Meeting held on 08th February, 2023 and case was approved. Accordingly, registration letter CT-0048 was issued on 22nd February, 2023.

2. Application for amendment in **Investigator's Brochure** (Version 5.0) and **Patient Material Submission** of subject trial, was received on 16th March, 2023, from Dr. Sayed Fasial Mahmood, PI of applied trial & Associate Professor & Section Head Infectious Diseases, Department of Medicine, The Aga Khan University Hospital, Karachi, Pakistan, Stadium Road, Karachi. Application is along with a fee of Rs. 25000/- deposited vide challan no. 7116343608, dated 08th March, 2023.

3. Application is reproduced as under:

Subject: *Amendments and patient Material submission of the study" A Phase 3, multicentre, randomized, double-blind, 24-week study of the clinical and antiviral effect of S-217622 compared with placebo in non-hospitalized participants with COVID-19 Reference No.: F. No.03-25/2023-CT(PS)*

S.No	***Document Name***	***Version Date***	***Version***
01	*Subject Case Report Forms ACTIV _2d_A5407 _ Version 4.0_27OCT2022 – Master dashboard ATD (Annotated)*	*27-Oct- 2022*	*4.0*
02	*Subject Case Report Forms ACTIV _2d_A5407 _ Version 4.0_27OCT2022 – Master dashboard ATD (Blank)*	*27-Oct- 2022*	*4.0*
03	***IB Edition 5 dated 07 Nov 2022***	***07-Nov- 2022***	***5.0***
04	*ACTIV-2d A5407 Participant Study Diary QL W10193_09Dec22_English (India)_ v3.0_21DEC2022*	*21-Dec- 2022*	*3.0*
05	*ACTG A5407 Participant Study Diary QLW10193_09Dec22_Urdu (Pakistan)_v3.0- II JAN2023*	*11-Jan- 2023*	*3.0*
06	*ACTIV-2d A5407 Participant Study Diary QLW10193_09Dec22_English (India)_ v3.0_21 DEC2022_ Tcert*	*21-Dec- 2022*	*3.0*
7	*Certificate_ACTG A5407 Participant Study Diary QLW10193_09Dec22_Urdu (Pak)*	*11-Jan- 2023*	*3.0*
8	*ACTIV-2d_A5407 STUDY PARTICIPANT MEDICATION LOG_V2.0 09Dec22_ (CC)*	*09-Dec- 2022*	*2.0*
9	*ACTIV-2d_AS407 STUDY PARTICIPANT MEDICATION LOG_V2.0 09Dec22_U R-PK (pdf)*	*09-Dec- 2022*	*2.0*
10	*ACTIV-2d_A5407 STUDY PARTICIPANT MEDICATION LOG_V2.0 09Dec22 ur-PK_ TCert*	*09-Dec- 2022*	*2.0*
11	*SCORPIO (ACTIV-2d) Locally Available COVID Treament_vl dated 9Jan2023*	*09-Dec- 2022*	*1.0*
12	*SCORPIO (ACTIV-2d) Locally Available COVID Treament_vl dated 9Jan2023 _ ur-PK_ clean*	*09 Jan 2023*	*1.0*
13	*SCORPIO (ACTIV-2d) Locally Available COVID Treament_vl dated 9Jan2023 _ur-PK_ TCert*	*09 Jan 2023*	*1.0*
14	*IQVIA eCOA Patient Manual Shionogi ACTIV 2d A5407 _Urdu(Pakistan)*	*13-Feb-2023*	*v1.0*
15	*Shionogi ACTIV _2d_AS407 _Urdu(Pakistan)_Main Menu*	*01-Feb-2023*	*v1.0*
16	*Shionogi ACTIV _2d_A5407 _Urdu(Pakistan)_post-Acute COV!D-19 Diary*	*30 Jan 2023*	*v9.0*
17	*Shionogi ACTIV _2d_A5407 _Urdu(Pakistan)_SF-36v2*	*17-Feb-2023*	*v10.0*
18	*Shionogi ACTIV_2d_AS407 _Urdu(Pakistan)_Symptoms Diary*	*30 Jan 2023*	*v9.0*
19	*Shionogi ACTIV_2d_AS407 _Urdu(Pakistan)_Training*	*30 Jan 2023*	*v9.0*
20	*Certificate_IQVIA eCOA Patient Manual Shionogi ACTIV 2d A5407 _ Urdu(Pakistan)_ vl.0_13 FEB 2023*	*17-Feb-2023*	*v1.0*
21	*Certificate_Shionogi ACTIV _2d_AS407 _Urdu(Pakistan)_EQ-5D· 5L_v1.0.0_24 FEB 2023*	*24-Feb-2023*	*v1.0*
22	*Certificate_Shionogi ACTIV _2d_A5407 _Urdu(Pakistan)_SF-36v2_v.1.0.0_24FEB2023*	*24-Feb-2023*	*v1.0*
23	*Certificate_Shionogi ACTIV _2d_A5407 _Urdu(Pakistan)_ vl.0.0_08FEB2023*	*15-Feb-2023*	*v1.0*
24	*eCRF Ver 5 Master dashboard_ATD*	*15-Feb-2023*	*v5.0*
25	*eCRF Ver 5 Unique Forms*	*15-Feb-2023*	*v5.0*
26	*Encouragement for early enrolment 12Jan2023*	*12-Jan-2023*	
27	*Shionogi ACTIV _2d_A5407 _Urdu(Pakistan)_EQ-5D-SL*	*17-Feb-2023*	
28	*Shionogi_Main V3.0PAK2.0_24Feb2023_CC_GS (Track changed version)*	*24-Feb-2023*	
29	*AKU-Shionogi_Main V3.0PAK2.0_24Feb2023_ur-PK (tracked changed version)*	*24-Feb-2023*	

Please also note that in the DRAP approval letter dated 22-Feb-2023 the following two sites were not listed.

i. ***National Hospital and Medical Centre***
ii. ***Akram Medical Complex***

I would like to request you to kindly share the status of the above mentioned two sites.
Please feel free to contact in case of any query.
Sincerely,

Decision: -

The CSC after detailed discussion and deliberation decided to approve the amendment in Investigator's Brochure (from Version 4.0 to Version 5.0) and Patient Material Submission. List of amended documents is as follows:

S.No	***Document Name***	***Version Date***	***Version***
01	*Subject Case Report Forms ACTIV _2d_A5407 _ Version 4.0_27OCT2022 – Master dashboard ATD (Annotated)*	*27-Oct- 2022*	*4.0*
02	*Subject Case Report Forms ACTIV _2d_A5407 _ Version 4.0_27OCT2022 – Master dashboard ATD (Blank)*	*27-Oct- 2022*	*4.0*
03	***IB Edition 5 dated 07 Nov 2022***	***07-Nov- 2022***	***5.0***
04	*ACTIV-2d A5407 Participant Study Diary QL W10193_09Dec22_English (India)_ v3.0_21DEC2022*	*21-Dec- 2022*	*3.0*
05	*ACTG A5407 Participant Study Diary QLW10193_09Dec22_Urdu (Pakistan)_v3.0- II JAN2023*	*11-Jan- 2023*	*3.0*
06	*ACTIV-2d A5407 Participant Study Diary QLW10193_09Dec22_English (India)_ v3.0_21 DEC2022_ Tcert*	*21-Dec- 2022*	*3.0*
07	*Certificate_ACTG A5407 Participant Study Diary QLW10193_09Dec22_Urdu (Pak)*	*11-Jan- 2023*	*3.0*
08	*ACTIV-2d_A5407 STUDY PARTICIPANT MEDICATION LOG_V2.0 09Dec22_ (CC)*	*09-Dec- 2022*	*2.0*
09	*ACTIV-2d_AS407 STUDY PARTICIPANT MEDICATION LOG_V2.0 09Dec22_U R-PK (pdf)*	*09-Dec- 2022*	*2.0*
10	*ACTIV-2d_A5407 STUDY PARTICIPANT MEDICATION LOG_V2.0 09Dec22 ur-PK_ TCert*	*09-Dec- 2022*	*2.0*
11	*SCORPIO (ACTIV-2d) Locally Available COVID Treament_vl dated 9Jan2023*	*09-Dec- 2022*	*1.0*
12	*SCORPIO (ACTIV-2d) Locally Available COVID Treament_vl dated 9Jan2023 _ ur-PK_ clean*	*09 Jan 2023*	*1.0*
13	*SCORPIO (ACTIV-2d) Locally Available COVID Treament_vl dated 9Jan2023 _ur-PK_ TCert*	*09 Jan 2023*	*1.0*
14	*IQVIA eCOA Patient Manual Shionogi ACTIV 2d A5407 _Urdu(Pakistan)*	*13-Feb-2023*	*v1.0*
15	*Shionogi ACTIV _2d_AS407 _Urdu(Pakistan)_Main Menu*	*01-Feb-2023*	*v1.0*
16	*Shionogi ACTIV _2d_A5407 _Urdu(Pakistan)_post-Acute COV!D-19 Diary*	*30 Jan 2023*	*v9.0*
17	*Shionogi ACTIV _2d_A5407 _Urdu(Pakistan)_SF-36v2*	*17-Feb-2023*	*v10.0*
18	*Shionogi ACTIV_2d_AS407 _Urdu(Pakistan)_Symptoms Diary*	*30 Jan 2023*	*v9.0*
19	*Shionogi ACTIV_2d_AS407 _Urdu(Pakistan)_Training*	*30 Jan 2023*	*v9.0*
20	*Certificate_IQVIA eCOA Patient Manual Shionogi ACTIV 2d A5407 _ Urdu(Pakistan)_ vl.0_13 FEB 2023*	*17-Feb-2023*	*v1.0*
21	*Certificate_Shionogi ACTIV _2d_AS407 _Urdu(Pakistan)_EQ-5D· 5L_v1.0.0_24 FEB 2023*	*24-Feb-2023*	*v1.0*
22	*Certificate_Shionogi ACTIV _2d_A5407 _Urdu(Pakistan)_SF-36v2_v.1.0.0_24FEB2023*	*24-Feb-2023*	*v1.0*
23	*Certificate_Shionogi ACTIV _2d_A5407 _Urdu(Pakistan)_ vl.0.0_08FEB2023*	*15-Feb-2023*	*v1.0*
24	*eCRF Ver 5 Master dashboard_ATD*	*15-Feb-2023*	*v5.0*
25	*eCRF Ver 5 Unique Forms*	*15-Feb-2023*	*v5.0*
26	*Encouragement for early enrolment 12Jan2023*	*12-Jan-2023*	
27	*Shionogi ACTIV _2d_A5407 _Urdu(Pakistan)_EQ-5D-SL*	*17-Feb-2023*	
28	*Shionogi_Main V3.0PAK2.0_24Feb2023_CC_GS (Track changed version)*	*24-Feb-2023*	
29	*AKU-Shionogi_Main V3.0PAK2.0_24Feb2023_ur-PK (tracked changed version)*	*24-Feb-2023*	

2. Further, the Committee also approved following two additional Clinical Trial Sites for the trial:

i. M/s Akram Medical Complex, Lahore
ii. National Hospital and Medical Centre, Lahore.

AGENDA ITEM XVIII:

APPLICATION FOR CLOSE-OUT OF A PHASE-III CLINICAL TRIAL TITLED, "AN INTERNATIONAL, MULTI-CENTER, CONTROLLED, RANDOMIZED CLINICAL TRIAL TO EVALUATE RIFAMPICIN 1200MG AND 1800MG DAILY IN THE REDUCTION OF TREATMENT DURATION FOR PULMONARY TUBERCULOSIS FROM 06 MONTHS TO 04 MONTHS" FORM AGA KHAN UNIVERSITY HOSPITAL F. NO.03-06/2018-DD (PS).

It is submitted that the subject Clinical Trial was placed before CSC in its 6th Meeting held on 20th January, 2020. The Committee decide the case as follows:

> *The CSC after deliberations approved the Clinical Studies/ Trial "To Evaluate Rifampicin 1200 Mg and 1800 Mg Daily in the Reduction of Treatment Duration for Pulmonary Tuberculosis from 06 Months to 04 Months (RIFA-SHOT)", to be conducted at Clinical Trial Unit, Aga Khan University Hospital, Karachi & Shaukat Khanum Memorial Cancer Hospital, Lahore.*
>
> *CSC also approved that locally manufactured IMP can be replaced with imported medicine, as requested & informed by the applicant".*

2. Accordingly, registration letter CT-0003 was issued on 12th February, 2020. The study was approved for 24 Months & for total enrolment of 100 subjects.

3. Application received from Dr. Bushra Jamil, Professor, Department of Medicine Aga Khan University, Karachi, dated 29th September, 2022. Wherein application is a **Close-Out** report along with processing fee of miscellaneous matter paid vide challan number 1451973572, dated 01st September, 2022.

4. Application and report is reproduced as under:

Sub: Notification of Study close-out.

Dear Sir,

We are submitting the study close-out report after notifying it to ERC and NBC for the acknowledgement of Drug Regulatory Authority for the study "An International Multicenter Controlled Clinical Trial to evaluate 1200mg and 1800mg rifampicin daily in the reduction of treatment duration for pulmonary tuberculosis from 6 months to 4 months." with DRAP reference no: 3-6/2018-DD(PS).

This study was sponsored by St. George's University of London, UK.

The close-out report of the study progress is provided along.

Please feel free to contact us if you require further information or in case of any query.

Best Regards,

Study Completion Report

An International Multicenter Controlled Clinical Trial to evaluate 1200mg and 1800mg rifampicin daily in the reduction of treatment duration for pulmonary tuberculosis from 6 months to 4 months.
ERC Project ID: 0905
DRAP Reference No: 3-6/2018-DD(PS)
NBC Reference No: 4-87 /NBC-329

RIFASHORT

This is an open-label 3-arm trial to compare a standard 6-month control regimen with two 4- month treatment regimens for the treatment of tuberculosis (TB).

Rationale and Aim:

The overall aims of the trial are:

i. *To determine whether an increase in the daily dose of rifampicin from the current WHO recommended dose to 1200mg or 1800mg would result in more rapid sterilization of the lungs and allow a reduction of treatment duration to 4 months.*
ii. *To assess whether the increased doses will result in an increase in severe (grade 3 or 4) adverse events and/or any serious adverse events (SAEs).*

Outcome measures:

Primary outcomes:

i. *Efficacy: the proportion with a combined unfavourable endpoint measured 18 months from randomisation; this endpoint includes loss to follow-up during treatment, failure at the end of treatment, recurrence and death. This will be measured in the modified intent-to-treat microscopy-positive population.*
ii. *Safety: occurrence of grade 3 or 4 adverse events at any time during chemotherapy and one-month post-therapy in the safety population with an MTBC positive test result in Xpert MTB/RIF positive population.*

Secondary outcomes:

i. *Per protocol analysis of the primary efficacy outcome.*
ii. *Combined unfavorable endpoint measured 18 months from randomisation in the Xpert MTB/RIF positive (i) modified intent-to-treat and (ii) per protocol populations*
iii. *Sputum cultures positive for M. tuberculosis at 8 and 12 weeks from randomisation*
iv. *Any adverse event, up to one month after completion of treatment, graded according to the DAIDS criteria (Appendix AS)*
v. *Time to unfavorable outcome in the modified intent-to-treat and per protocol sputum smear microscopy-positive population.*

Pakistan Study Site (Aga Khan University Hospital) Summary:

i. *Total number of subjects screened: 32*
ii. *Total number of subjects enrolled: 30*
iii. *Total number of subject's screen failed: 02*
iv. *Total number of subjects withdrawn: 05*
- *02 subjects withdrew due to non-compliance*
- *3 subjects withdrew due to late exclusions upon medical conditions developed as Empyema, ileocecal TB and SAE/NAE of high bilirubin.*

v. *Total number of subjects completed the study: 25*
vi. *Number of subjects relapsed: 01 relapse case in a follow up phase*
vii. *Total number of SAEs/NAEs: 03*

S. No.	***SAE/NAE***	***Event***
i.	*SAE*	*High Bilirubin*
ii.	*SAE*	*Anemia*
iii.	*NAE*	*Pregnancy*

viii. *Total number of protocol deviations: 10*
- *Minor: 07*
- *Moderate: 03*
- *Major: none*

S.No.	Priority	Description
i.	*Moderate*	*Patient 001 has been mistakenly dispensed Rifinah 150 instead of Rifadin due to lookalike medicines. The patient was immediately called and wrong medication was replaced with the correct one.*
ii.	*Minor*	*General gram staining was done on sputum sample instead of AFB for the visit 0 of patient 001 and measures were taken to mention the correct lab test on the lab slips.*
iii.	*Minor*	*Blood sample of patient 005 for visit 2 was not enough to run the test. Patient was counselled to rehydrate and be prepared before the sampling.*
iv.	*Minor*	*Patient 007 was unable to produce enough sputum sample for visit 1 to run the test. Patient has been counselled to get sufficient sample and normal saline nebulization was suggested.*
v.	*Minor*	*Sputum sample of patient 025 for visit 1 was not enough to run the test. Patient has been counselled to get sufficient sample and normal saline nebulization was suggested.*
vi.	*Minor*	*Patient 026 was not able to produce enough sputum for visit 1. Patient has been counselled to get sufficient sample and normal saline nebulization was suggested.*
vii.	*Minor*	*Sputum sample of patient 026 for visit 4 was leaked out of the container due to improper handling. Patient has been educated about the proper handling of sample container.*
viii.	*Moderate*	*60 doses of medicine were mistakenly dispensed instead of 56 doses, to patients 001 and 002, Patients were contacted and asked to return the extra doses.*
ix.	*Minor*	*Patient 003 and 008 were dispensed with 120 doses mistakenly instead of 112 doses. Patients were contacted and asked to return the extra doses.*
x.	*Moderate*	*GeneXpert test of patients 007, 008, 029 and 030 were not performed on the screening visit as it was performed outside of AKU. Study staff was retrained to conduct all the prerequisite tests.*

Study Close-out Monitoring:

- *The remote monitoring of study is completed by sponsor with the site during April 2022 to June 2022.*
- *Official close-out meeting was held on 29th June'2022 followed by issuance of official study-end letter by the sponsor.*

Work to be done next year:

- *The data analysis will be performed by the sponsor and the results will be shared through the publication.*

Unused Investigational Product to Incinerate

As per sponsors recommendation, we have to incinerate the remaining expired, unused investigational product of the above mentioned trial for which we are seeking DRAP approval.

Following is the information related to the investigational product:

S.No.	Description	Quantity unused
i.	*Rifin Forte*	*6038 Tablets*
ii.	*Rifinah 150*	*2682 Tablets*
iii.	*Rifadin 300mg*	*772 Tablets (Quarantined)*

5. Applicant may be asked to furnish all record regarding IMPs import and trial extension as the trial was approved for only 24 Months (w.e.f. 12th February 2020), whereas close-out report is furnished on 29th September, 2022 (after 07 months from trial expiry date)

6. Submitted for consideration of Clinical Studies Committee & for constitution of expert panel for GCP Compliance/IMPs reconciliation panel as per DRAP approval/registration, who after reconciliation may also accompany during incineration process.

Decision:

The CSC after detailed discussion and deliberation decided that, the Chairman CSC constitute an expert panel for GCP-Compliance Inspection of the trial titled, "An International, Multi-Center, Controlled, Randomized Clinical Trial to Evaluate Rifampicin 1200mg and 1800mg Daily in the Reduction of Treatment Duration for Pulmonary Tuberculosis from 06 Months to 04 Months", and for reconciliation of IMPs as per DRAP approved quantities.

2. Further, it was decided that, the expert panel will also accompany the process of incineration of following mentioned IMPs after reconciliation with record:

S.No.	***Description***	***Quantity unused***
i.	*Rifin Forte*	*6038 Tablets*
ii.	*Rifinah 150*	*2682 Tablets*
iii.	*Rifadin 300mg*	*772 Tablets (Quarantined)*

3. After destruction/incineration a complete GCP-Compliance, Drug Reconciliation & Destruction report will be submitted to the CSC for consideration.

4. Moreover, applicant/PI directed to furnish all record to Pharmacy Services Division regarding IMPs import and trial extension as the trial was approved for only 24 Months (w.e.f. 12th February 2020), whereas close-out report was submitted on 29th September, 2022 (after 07 months from trial expiry date).

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