DRAFT MINUTES OF THE 41ST MEETING OF THE CLINICAL STUDIES COMMITTEE TO BE HELD ON 10TH APRIL, 2023.

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The 41st meeting of the Clinical Studies Committee was held on 10th April, 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. The meeting was attended by the following members: -

Sr. No.	Name	Designation
01	**Dr. Obaidullah**	Director Pharmacy Services Division **Chairman CSC**,.
02	**Ahsan Ul Haq Athar**	Deputy Director, Pharmacy Services Division **Secretary, CSC**.
03	**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.

3. Following members attended the meeting online through Zoom:

01	**Prof. Dr. Fazal Subhan**	Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar, Khyber Pakhtunkhwa.	Member
02	**Prof. Munawar Alam Ansari.**	Professor of Pharmacology, Dean Faculty of Pharmacy, Liaquat University of Medical Sciences, Jamshoro. **(Sindh)**	Member
03	**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
04	**Dr. Faiza Bashir**	Chairman, Pakistan Health Research Council or his/her nominee, Islamabad.	Member
05	**Mr. Waqas Latif**	Data Analyst/Biostatistician in Quality Enhancement Cell (QEC) at University of Health Sciences, Lahore, Punjab.	Member

2. Mr. Nouman Yousuf, Hafiz Muhammad Jawad Ali, Malik Muhammad Asad and Shafqat Hussain Danish assisted the Committee and Secretary in presentation of the agenda. Dr. Sadia Asim attended the meeting as observer on behalf of PPMA.

AGENDA ITEM I:

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.*

8. The decision of CSC was communicated vide this office letter F. NO. 16-40/2023-CSC dated 21st March 2023. The applicant has replied as following to the queries of the CSC.

9. Reference is made to comments (F. No. 16-40/2023-CSC) received from Drug Regulatory Authority Pakistan after the Clinical Studies Committee's (CSC) 40th meeting held on 17th March 2023 for clinical trial titled, "A phase III randomized, double-blind, placebo-controlled study to evaluate the effect of Bi- 26 (strain of *Bifidobacterium longum*, *B. infantis*) supplementation vs. placebo on weight gain on underweight infants". The Agency's queries are shown in bold font. Bill &

Melinda Gates Medical Research Institute (Gates MRI) provides responses to these queries below in plain font:

Query 1: As there are no completed clinical studies with Bi-26 as of the time of this IB addendum and two studies with Bi-26 are ongoing. Is there any particular clinical/safety study of Bifidobacterium Longum subspecies infantis strain Bi-26?

To address this request and supply relevant information regarding safety of the product, the Sponsor is providing the following elements of support which will be elaborated upon in more detail in the subsequent paragraphs. Please also refer to Sections 6.2 and 6.3 of the IFF IB in addition the Sponsor's IB addendum for safety information.

• Completed clinical studies in which Bi-26™ was administered as part of multi-strain probiotic products did not identify safety concerns

• In the ongoing IMPROVE study, in which Bi-26™ is administered as a single strain, an interim safety analysis revealed that Bi-26™ has been well tolerated

• Data from commercially available use of Bi-26™ containing products, including in extremely preterm and low birth weight infants in the neonatal intensive care unit (NICU) setting, support the overall safety of Bi-26™ in these very vulnerable infants

1. Completed clinical studies with Bi-26: No safety concerns noted when administered as part of a multi-strain probiotic

The IFF IB, ed. 3, summarizes several completed studies in which Bi-26™ was administered as a component of a multi-strain probiotic product.

• Sowden et al. published a study on a multi-strain probiotic on the incidence and severity of necrotizing enterocolitis (NEC) and feeding intolerances in preterm neonates. According to the probiotic manufacture's LabinicTM (Biofloratech, Surrey, UK) webpages, Bi-26™ is part of this multi-strain consortia together with Lactobacillus acidophilus NCFM and Bifidobacterium bifidum
Bb-06 (https://www.biofloratech.com/Health_Professionals.html). The study found that this multispecies probiotic is a safe and cost-effective way of preventing NEC and feeding intolerances
in neonates.

• According to LabinicTM webpages, Bi-26™ has also been part of the same consortia in a large observational study. Here, Robertson et al. compared the rates of NEC, late-onset sepsis, and mortality in 5-year epochs before and after implementation of routine daily multi-strain probiotics administration in high-risk neonates. They used two different multi-strain products and Bi-26™ was
part of the latter product. The study found that the administration of multispecies Lactobacillus and Bifidobacterium probiotics was associated with a significantly decreased risk of NEC and late-onset
sepsis in the neonatal unit, and no safety issues were found with the administration of either multispecies Lactobacillus and Bifidobacterium probiotics to very low birth weight infants.

• A small study has already evaluated Bi-26™ in probiotic consortia combined with fructooligosaccharides (FOS) on modulating autism spectrum disorders (ASD) (in children aged 3-9 years) related behavior, gut microbiota, short chain fatty acids (SCFAs) and neurotransmitters (14). The intervention in this study time varied from 30 to 108 days, and the consortia consisted of Bi-26™, *Lacticaseibacillus* (former Lactobacillus) *rhamnosus* HN001, *Bifidobacterium lactis* BL-04, and *Lacticaseibacillus* (former Lactobacillus) *paracasei* LPC-37 (1010 CFU/day) together with FOS
(FOS dose not reported in the article (Wang et al). The study found the intervention was well tolerated with no adverse event (AE) associated with administration or no gastrointestinal (GI) intolerance or allergic responses reported during the study.

• Another study assessed the 12-strain probiotic blend including Bi-26™ (and strains of *B. bifidum*, *B. breve*, *B. lactis*, *B. longum*, *L. acidophilus*, *L. casei*, *L. paracasei*, *L. plantarum*, *L. reuteri*, L. *rhamnosus*, *L. salivarius*; 1010 CFU/day) with XOS in reducing self-assessed immune and GI symptoms and impacting the Quality of Life (QoL) parameters in healthy adults (Snigdha et al.). Safety related data was not reported in the article, but a 3-month open label multi-strain symbiotic intervention attenuated digestive health issues, reduced the number of sick days and number of days
taken off work, and improved QoL as indexed by self-reported questionnaires.

In addition to the aforementioned completed clinical trials with Bi-26™, please also refer to Table 4 in the IFF IB which summarizes clinical trials with *B. infantis* supplementation regardless of strain. Of note, several studies are included in that table for which the dose of *B. infantis* administered overlaps with the range of doses in trial Gates MRI-MNK01-301 (see Query 3 response), including a study of EVC001 in which neonates received 18 to 28 billion CFUs of EVC001 for 21 days (Smilowitz et al).

2. Ongoing IMPROVE Study: Bi-26 at dose of 4.2B CFUs x 7 days is well tolerated in neonates in interim safety analysis

As noted in the IFF IB, ed. 3, data from an interim safety analysis were provided from the ongoing double-blind, randomized-controlled IMPROVE study in Papua New Guinea. In this study, Bi-26™ is one of 3 treatment arms and is administered at 4.2 billion CFUs in combination with a human milk
oligosaccharide to neonates <72 hours after birth. Per the IMPROVE team, the analysis of the first 59 infants enrolled showed that all children tolerated the treatment well. Based on the 1:1:1 randomization scheme, we estimate that ~19 or 20 infants will have received Bi-26™ at the time of the interim safety analysis. As Gates MRI is not the Sponsor of this study, we are unable to provide more details at this time.

3. Commercial Use: Use of Bi-26™ containing products, including in extremely preterm and low birth weight infants in the NICU setting, support the overall safety of Bi-26

As reported by IFF in their IB, Bi-26™ has been sold worldwide, including in North America, China, South Africa, Middle East, Europe, and Asia/Pacific countries. Over 23,000 kg of Bi-26TM has been sold since 2012; IFF affirms that no safety-related complaints related to Bi-26™ have been received.

Although Bi-26™ is not commercially available as a single strain or at the dose intended for use in the CONSTELLATION study, it is commercially available in combination with other probiotics which contributes safety experience in large numbers of infants, including extremely vulnerable infants in the NICU, and therefore allows for the potential for identification of rare events that would be difficult to observe in clinical trials.

Premature infants have high rates of sepsis, gastrointestinal complications such as NEC and mortality. While the exact etiology for these events is unknown, immaturity of the gastrointestinal tract with increased permeability and immaturity of the immune system are contributors. In recent years there has been increased routine use of oral probiotics in preterm infants in the NICU setting to prevent NEC and sepsis and improve mortality even though, these infants are also at greater risk of bacterial translocation and possible probiotic-associated bacteremia or sepsis.

This practice of routine probiotic administration has been in place at the Norfolk and Norwich University Hospital for the past 10 years and since 2016, the probiotic administered has been commercially available Labinic Drops™ (Biofloratech, UK) which provide ~2 billion colony forming units (CFU) of live bacteria (*Lactobacillus acidophilus* 0.67 x 109 CFU, *Bifidobacterium bifidum* 0.67 x 109 CFU, and *Bifidobacterium longum* subsp. *infantis* Bi-26TM 0.67 x 109 CFU) (Acuna-Gonzalez et al. 2023).

Similar to other cases of probiotic strain bacteremia, a case of bacteremia with Bi-26™ at this hospital occurred in a pre-term infant (24 weeks and 4 days' gestation) with extremely low birth weight (490 g) who had a complicated clinical course including need for respiratory support and gastrointestinal complications requiring surgical intervention. In this case, blood cultures were taken and empiric antibiotics initiated due to an unexpected increase in C-reactive protein. The infant had other laboratory abnormalities (leukocytosis, neutrophilia, thrombocytopenia) but no overt clinical signs or symptoms of infection. Comparative genomics were subsequently utilized to confirm that the *B. infantis* isolated from the blood culture originated from the probiotic formulation. The bacteremia resolved quickly following antibiotic administration; blood cultures taken 3 days after the positive result were negative for Bifidobacterium species. The evolving gut pathology in this case (spontaneous ileal perforation) most likely served as the entry point for translocation of Bi-26™ into the bloodstream. The infant was discharged home 7 months after birth.

As noted by the authors, case reports of probiotic associated bacteremia/sepsis are extremely rare. The authors estimate globally that hundreds of thousands of preterm infants will have now received multiple doses of prophylactic probiotics while in the NICU. In their own decade long experience in which over 1000 infants have been treated with typically 30 to 60 days of Bifidobacterium-Lactobacillus probiotics, this is the first case report of probiotic associated bacteremia. Per the manufacturer's website (Labinic Drops - Information for Health Professionals (biofloratech.com)) over 2 million doses of Labinic Drops have been given to date (2023). The website notes only the single case report of Bi-26™ bacteremia described above. Bi-26™ does not bear acquired antibiotic resistance and remains susceptible to common antibiotics (IFF IB, Section 4.2.1 Antibiotic Resistance Patterns) which is important in case of a rare event of Bi-26™ bacteremia or sepsis such as the one described by Acuna-Gonzalez et al. This case was identified by the Sponsor through a literature review undertaken as part of routine pharmacovigilance activities to evaluate, on an ongoing basis, investigational products being administered in clinical studies. Bacteremia with *B. infantis* strains was already recognized as a rare possible risk in the CONSTELLATION study documents. Although this event does not change the overall safety profile for Bi-26™ or the benefit risk assessment for use of Bi-26™ in underweight infants, the Sponsor IB addendum, IFF IB, and ICF will be updated to reflect the occurrence with Bi- 26™.

In summary, available clinical trial data on Bi-26™ administered as a single product or as part of a combination of multiple probiotic strains has not identified any safety concerns. There has been considerable commercial use of Bi-26™ as part of multi-strain probiotic products. The experience to date with Bi-26™ is similar to other probiotic strains, including other *B. infantis* strains. There is a risk of probiotic-associated bacteremia and sepsis.

The literature from the commercial experience demonstrates that these events of bacteremia and sepsis are rare, even in the vulnerable NICU infants who are at greater risk of bacterial translocation, and can be treated with antibiotics. The events primarily occurred in neonates who were extremely-low to low birth weight who had associated comorbidities, received respiratory assistance in the NICU, had impaired immune systems and risk factors for leaky gut that could lead to bacterial translocation (e.g. bowel perforations). The Gates MRI-MNK01-301 Phase 3 study requires infants to be at least 30 days of age, admitted for an acute non-surgical illness, and must have been discharged from the hospital before they receive Bi-26™. Additionally, infants cannot have any congenital conditions likely to interfere with normal growth and development. Infants are also excluded if they have not been discharged from the hospital since birth or have not been at home for at least one week since birth or experienced septic shock or required mechanical ventilation during the hospitalization that qualified the infant for study inclusion. Thus, the current study criteria exclude participants who are most at risk to experience *B. infantis* bacteremia and sepsis. As an additional safety measure, an Independent Monitoring Committee will review unblinded data on an ongoing basis and make recommendations about the conduct of the study to the Sponsor. To provide further oversight of the safety of infants participating in the study, the Sponsor will review blinded study data and perform ongoing literature reviews to identify relevant safety information.

References

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Robertson C, Savva GM, Clapuci R, Jones J, Maimouni H, Brown E, et al. Incidence of necrotising enterocolitis before and after introducing routine prophylactic Lactobacillus and Bifidobacterium probiotics. Archives of Disease in Childhood – Fetal and Neonatal Edition. 2020;105(4):380.
Smilowitz JT, Moya J, Breck MA, Cook C, Fineberg A, Angkustsiri K, et al. Safety and tolerability of Bifidobacterium longum subspecies infantis EVC001 supplementation in healthy term breastfed infants: a phase I clinical trial. BMC pediatrics. 2017;17(1):133.
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Wang Y, Li N, Yang JJ, Zhao DM, Chen B, Zhang GQ, et al. Probiotics and fructo-oligosaccharide intervention modulate the microbiota-gut brain axis to improve autism spectrum reducing also the hyper-serotonergic state and the dopamine metabolism disorder. Pharmacol Res. 2020;157:104784.

Query 2: 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.

The Sponsor acknowledges that Phase 1 and 2 studies have not been conducted with *B. infantis* strain Bi-26™, and provides the below rationale to apply the clinical safety data from EVC001, a genetically similar *B. infantis* strain, as supportive evidence to initiate the Phase 3 trial Gates MRI-MNK01-301. Our rationale in support of initiation of the proposed Phase 3 trial is summarized below (reference is made to Sponsor Response dated 1 March 2023):

• *B. infantis* strain Bi-26™ is a dietary supplement and not a medicinal drug. Clinical trials evaluating medicinal drugs under an Investigational New Drug Application (IND) must be conducted under US FDA oversight. In contrast, INDs are not required for clinical trials of dietary supplements unless the product makes claims to diagnose, cure, treat or prevent disease. The probiotic is considered a dietary intervention (a human food product) to be evaluated for supporting weight gain in underweight children.

• *B. infantis* strains are commensal bacteria isolated from humans that have historically been considered non-pathogenic, safe and suitable for human consumption (refer to IFF IB, Section 6.3 Marketing Experience).

• *B. infantis* exists naturally in the guts of infants in LMICs with peak presence in infants of the same age as the population for the proposed Gates MRI-MNK01-301 Phase 3 trial.

• *B. infantis* strain Bi-26™ is a bacterium that is generally recognized as safe (GRAS) (refer to the previously provided GRAS Notice GRN 00985 and Sponsor Response dated 8 March 2023). FDA has defined "safe" as a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use. Note that *B. infantis* strain EVC001 also carries the GRAS designation.

• The SYNERGIE Phase 2 study (Barratt 2022) evaluated *B. infantis* strain EVC001, which is genetically similar to Bi-26™ in infants, with severe acute malnutrition. This trial showed an increase in fecal *B. infantis* EVC001 and increased weight gain in infants who received EVC001. No safety concerns were reported (refer to IB addendum, v2, Section 6.2).

• The nucleotide sequences of *B. infantis* strains Bi-26™ and EVC001 were compared using the FastANI program. This method measures the percentage of genomes where shared nucleotide sequences are identical (Jain 2018). This analysis determined that the average nucleotide identity between Bi-26 and EVC001 is 98.2% which indicates a very high level of similarity (Gates MRI, unpublished data).

• A clinical trial IMPROVE evaluating Bi-26™ is currently ongoing in Papua New Guinea. The study is testing two formulations, including Bi-26™ at 4.2 billion CFU per dose, relative to a control on feasibility and safety, and possible beneficial impact on nasopharyngeal colonization and vaccine response in newborn babies (see Response to Query 1 for details). IMPROVE interim safety analysis of the first 59 infants shows that all children tolerated the treatment well (refer to IFF IB, edition 3, section 6.2 Safety and Efficacy).

• *B. infantis* strains, including Bi-26™, have been administered to preterm and very low birth weight infants with no safety concerns reported (see Response to Query 1 and Manufacturer's IB, section 6.2).

Due to the similarity of the EVC001 and Bi-26™ strains at the genetic level, the predictive inherent safety of *B. infantis* strains (commensal organisms, GRAS status, long historical safe use in food products), the data from the SYNERGIE study (Barratt 2022) and the available safety information for Bi-26™ from clinical and commercial use, provide sufficient supportive information for this dietary supplement to proceed to Phase 3 to obtain confirmatory data on efficacy and safety for *B. infantis* Bi- 26™ to address the significant unmet medical need for a dietary intervention for underweight infants.

Jain, C, et al. (2018). "High throughput ANI analysis of 90K prokaryotic genomes reveals clear species boundaries." Nature Communications, https://doi.org/10.1038/s41467-018-07641-9

Query 3: 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

Bifidobacterium longum ssp. *infantis* strain Bi-26™, proposed for use in study Gates MRI- NK01-301, is classified as a probiotic dietary supplement. In the USA, dietary supplements, including probiotics, are controlled by United States Food and Drug Administration (US FDA) under the Dietary Supplement Health and Education Act of 1994 (DSHEA). However,

because dietary supplements are considered human food products rather than medicinal drugs, they do not require US FDA approval prior to marketing the product. Manufacturers are prohibited from making any claims for Dietary Supplements to diagnose, cure, treat or prevent disease. Although it is permitted to make general structure/function claims for Dietary Supplements.

While the manufacturer IFF/Dupont recently received US FDA GRAS designation status for Bi-26™ under its intended condition of use (an estimated daily intake at the mean of 10^9 to 10^{10} CFU and 1.67 x 10^{10} CFU at the 90th percentile of Bi-26/day for infant formula in healthy term infants) (GRAS Notice No. 000985) (refer to Sponsor Response dated 8 March 2023), the GRAS designation supports safe use of Bi-26™ in other probiotic single-strain or multi-strain dietary supplement products including those aimed at infants and children.

Subsequent DRAP clarification received on 29 March 2023: ***If our proposed IP "Bi-26" already available in any market for any other brand name in same indication, kindly share their product details. As the Gate foundation is not a manufacturer, then what is the relationship between the manufacturing facility and Gates for this study.***

Bi-26™ is an investigational probiotic dietary supplement that is currently not commercially marketed as a stand-alone, single-strain product in any country worldwide but is available as part of multi-strain probiotics such as Labinic Drops (refer to Response to Query 1). For clarification, IFF is an independent manufacturer who has a portfolio of probiotic products, including Bi-26™, for use in dietary supplements. IFF provides their bulk products to customers who may in turn create their own custom dietary supplements for sale as over the counter products.

Additionally, IFF may at its discretion enter into agreements to provide material to support clinical trials from various trial Sponsors. Gates MRI, a not-for-profit organization, engaged IFF as a contract manufacturing organization (CMO), to manufacture Bi-26 clinical trial material for the Phase 3 trial.

Gates MRI is the clinical trial Sponsor for only the Phase 3 Gates MRI-MNK01-301 study. As such, Gates MRI does not have access to data from other trial Sponsors working with IFF or from trial Sponsors who use over the counter products as their clinical trial material. Therefore, Gates MRI cannot provide information on studies for which it is not the trial Sponsor beyond what is summarized in the IFF IB or available in the published literature.

Query 4: Clarification regarding Bifidobacterium Longum subspecies infantis (Bi-26 strain) in Colony Forming units (CFU) for already approved indications (if any) and current study.

Bi-26™ is an investigational probiotic dietary supplement that is currently not commercially marketed as a stand-alone, single-strain product in any country worldwide, but is available as part of multi-strain probiotics such as Labinic Drops in the United Kingdom and a number of African countries (refer to the manufacturer's website for Labinic Drops - Information for Health Professionals (biofloratech.com)).

The clinical trial material (CTM) for study Gates MRI-MNK01-301 was formulated to contain a minimum dose of ~25 billion CFUs/1g sachet at time of manufacture. The target formulated dose was selected in consideration of the product stability profile of a live bacterial product and the expected decrease in CFUs over the duration of the clinical study. The target formulated dose also ensures, with 95% confidence, that the minimum dose contained within each sachet will be 5 billion CFUs or greater over the 24-month shelf life of the product.

The CFU content at the time of release is the maximum CFU for the CTM throughout its shelf life as indicated in the representative product stability profile(s) (see Shelf-Life Stability Justification document provided in the initial submission). As the CTM will not be used in the clinical study immediately after manufacture due to time required to obtain regulatory approvals for the trial, package and ship clinical material, the dose is expected to be less than the CFU at time of CTM release but within the shelf life specification (≥ 5 billion CFU/1g).

Subsequent clarification provided on 29 March 2023 by DRAP: ***Any supporting documents that Bifidobacterium Longum is belongs to same strain of Bi-26 and the studies and registered products (if any) available in market.***

Per IFF's IB, ed, 3, Section 4.1.2 (pages 12-13), the Bi-26 strain taxonomic identity was verified by complete genome sequencing of Bi-26™. For ease of reference, we have provided the relevant information from the IB in the response below.

"Complete genome sequencing was conducted in addition to the full-length sequencing of the 16S rRNA gene of Bi-26™ resulting in 1 contig and no plasmids. The genome is 2.6Mb is 59.3% GC, has 2,411 coding sequences (CDS), 12 rRNA genes, and 57 tRNA. The average nucleotide identity (ANI) of Bi- 26™ to the type strain, *B. longum* ssp. *infantis* ATCC 15697, is above 99% confirming the sub-species identification of Bi-26™ as *B. longum* ssp. *infantis.*

To further establish the taxonomic identity of Bi-26™, a phylogenetic tree of *B. longum* species was built on 500 core proteins using RAxML in PATRIC database. This tree clearly demonstrates the three sub-species of *B. longum* and Bi-26™ clusters with other species of *B. infantis* including the type strain (see Figure below). This tree clearly demonstrates the three sub-species of *B. longum* and Bi-26™ clusters with other species of *B. infantis* including the type strain ATCC 15697. These data further clearly show that Bi-26™ belongs to the same species *Bifidobacterium longum*".

Query 5: Approval of subject clinical trial in Australia, New Zealand and Ghana as informed by the applicant during the meeting as not mentioned in application.

Subsequent clarification provided by DRAP on 29 March 2023: Is there any study available that is mentioned by PI during the meeting, if yes that belongs to same PI strain, kindly share as a support.

Please refer to response to Query 1 for a description of the IMPROVE trial that studies Bi-26™ as a single strain product in neonates.

The Sponsor would like to clarify that the IMPROVE clinical study referenced in IFF IB, Ed.3 and Sponsor's Bi-26™ Investigator's Brochure, Addendum 1, version 2, is conducted in Papua New Guinea.

This trial is listed on the Australian New Zealand Clinical Trials Registry (ANZCTR). The IMPROVE trial: IMpact of PRObiotic interVEntion in Papua New Guinean newborns. Registration number ACTRN12620001369910 Last updated 21 Dec 2020.
https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620001369910.
The information provided on the Registry indicates that this trial received approvals from the Papua New Guinea Institute of Medical Research Institute Review Board, Goroka, Papua New Guinea (approval on 7 December 2018) and the Papua New Guinea Medical Research Advisory Committee (MRAC), Waigani 131 NCD, Papua New Guinea (approval on 7 January 2019).
Please note that Gates MRI is not the Sponsor of the clinical trial IMPROVE and thus cannot provide more details on regulatory approvals.

06 April 2023 RE: Gates MRI-MNK01-301 Clinical Trial Application – Bullet Points for DRAP Meeting 1) The availability of Phase 1 and Phase 2 study for the Bi-26 strain only

- The Phase 1 or 2 is not required in Probiotic studies. However, some sponsor tags their studies as Phase 1 and 2 due to marketing purpose only.
- Bi-26 is administered without other probiotics in the IMpact of PRObiotic interVEntion in Papua New Guinean Newborns study (IMPROVE study, not sponsored by Gates MRI, phase reported as not applicable by the sponsor on clinical trials registry)
- Primary outcomes are feasibility of daily administration and safety (intolerance or probiotic sepsis, leading to cessation of supplementation)
- Available interim safety analysis on first 59 infants, based on randomization scheme, estimate ~19 or 20 infants received Bi-26.
- Infants tolerated the treatment well, no cases where a child vomited immediately after the treatment or report of immediate reaction post-treatment
- Registry reference: ICTRP Search Portal (who.int) 2) The guideline in support of Probiotics clinical Trials
- Probiotic dietary supplements are classified as a Food Substance and are regulated by the Center for Food Safety and Applied Nutrition, CFSAN, a branch of US FDA. • Only limited US FDA Guidance's for Industry are available for food and dietary supplements mainly for required cGMPs, product claims and label information.
- On the US FDA website for Dietary Supplements (https://www.fda.gov/food/dietarysupplements), the following is stated: o Thus, it is the Manufacturer of dietary supplements that is responsible for the safety of the products. US FDA will take action if consumer complaints are received that indicate the product is unsafe. o The safety of probiotic bacterial strains in dietary supplements is based on the FDA GRAS designation.
- US FDA provides guidelines for Dietary Supplements on their website "Questions and Answers on Dietary Supplements (excerpts from this website at https://www.fda.gov/food/information-consumers-using-dietary-supplements/questionsand-answers-dietary-supplements):

o "Under the Dietary Supplement Health and Education Act (1994) (DSHEA), FDA does not have the authority to approve dietary supplements before they are marketed. Generally, a firm does not have to provide FDA with the evidence it relies on to substantiate safety before or after it markets its products." o "By law, FDA does not approve dietary supplements or their labeling….

Based on the above, US FDA does not approve probiotic dietary supplements prior to marketing. Therefore, clinical trials are not required to demonstrate safety or efficacy because FDA does not require the submission and review of a marketing application prior to commercialization. This is in contrast to Medicinal Products that require submission and review of a Market Authorization Application by US FDA. 3) Safety data of Bi-26 is confirmed by US FDA GRAS designation.

- The safety of probiotic strains in dietary supplements is often based on GRAS designation issued by US FDA in the form of GRAS Notices (for example, GRAS Notice GRN 00985 for B. infantis strain Bi-26).
- GRAS designation can be obtained by different processes: o The manufacturer voluntarily submits a probiotic strain GRAS Monograph to US FDA, US FDA reviews the Monograph per scientific procedures and if FDA issues a letter with no questions about safety or legal issues, GRAS designation is obtained (this process was followed for Bi-26 by IFF); o Alternatively, as stated in 21CFR170.35 "The FDA Commissioner on his own initiative, may affirm that a substance that directly or indirectly becomes a component of food is GRAS under the conditions of its intended use".

♣ The path outlined in 21CFR170.35 is rarely applied and thus most GRAS Notices issued by US FDA includes this general statement "This letter is not an affirmation that B. longum ATCC SD 6720 is GRAS under 21 CFR 170.35" as a disclaimer to confirm that the FDA Commissioner did not initiate GRAS status request for this food substance/probiotic/dietary supplement. Reference: 21CFR 170.35: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-B/part170/subpart-B/section-170.35 4) If the Phase I and II not required for Probiotics, then why EVC001 and Synergy Study tagged as Phase I and II

- Companies will conduct clinical trials on probiotics to support product health claims by including statements such as "Product was evaluated in clinical trials" in labels and advertising materials to increase customer confidence.

o As example, please see the Evivo product (the EVC001 commercial product) at https://www.evivo.com/ that states: "Evivo works instantly and is clinically proven to reduce bad bacteria in your baby's gut by 80% replacing it with B. infantis EVC001, the good bacteria baby needs".

- Academics may conduct studies that inform their research areas of interest

Studies help provide information on potential benefits and uses in specific populations even if not required by regulators. As an example, the goal of the Gates MRI Phase 3 study is to provide data to inform a possible WHO recommendation for use of probiotics in underweight infants

Not all studies of probiotics have a phase assigned as this is not required. However, Sponsors may choose to categorize probiotic trials by assigning a phase similar to what is done for medicinal products. Assigning a trial, a phase helps succinctly communicate study objectives. For example, designating a study phase 1 makes it clear the primary objective is safety whereas a phase 3 designation indicates a study statistically powered to achieve an efficacy objective.

As per Discussion with DRAP, the DRUG act of Pakistan, not 100% applicable on our Probiotics study approval.

10. Secretary CSC presented the case before the Committee.

Decision:

The CSC after detailed deliberation, discussion and considering the reply submitted by the applicant decided to:

i. *Approve the Phase-III 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" under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site(s):*
   a. *Aga Khan University, Karachi*
   b. *The Central Park Teaching Hospital, Lahore.*
   c. *Shifa International Hospital, Islamabad.*
   d. *Avicenna Medical College and Hospital, Lahore*
   e. *Al-Shifa Research Center, Al-Shifa Trust Eye Hospital, Rawalpindi.*
   f. *Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad.*
   g. *Maroof International Hospital, Islamabad*

ii. *Direct the PI to closely monitor trial subjects and maintain follow-up record to ensure the safety of the trial participants (Infants) and PI will submit trial progress report fortnightly after endorsement from Data Safety & Monitoring Board/Committee.*

iii. *Approve the following quantities of IMPs to be imported:*

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)*	

AGENDA ITEM II:

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. **i.** Dr. Sidrah Nausheen (PI) (117-139/Corr.) **ii.** Dr. Sajid Sufi (Co-PI) (140-179/Corr.) **iii.** Dr. Shabina Ariff (Co-PI) (180-210/Corr.) **iv.** Dr. Lumaan Sheikh (Co-PI) (211-237/Corr.)
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following are need to be provided: i. Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.

		ii. Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India iii. Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia * GMP certificate of all manufacturer issued by respective country drugs regulatory body need to be provided. ** Further, connection & role of mentioned manufacturers need to be provided.
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Summary of IB is attached only for esomeprazole manufactured by M/s Ranbaxy Australia
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	200 Subjects on both site in Pakistan. Details regarding Subjects to be enrolled in Australia need to be provided.
19	Name of Monitors & Clinical Research Associate	Attached
20	Evidence of registration in country of origin.	TGA public summary is attached
21	Copy of registration letter (if registered in Pakistan)	Not applicable.
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	Approximately 03 Years.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings are recorded:

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

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

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

iv. GMP certificate of following manufacturer issued by respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided.
   a. Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.
   b. Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India
   c. Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia

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

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

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

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

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

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

Decision:

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

i. *As per provided documents, composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval.*
ii. *As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.*
iii. *AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials.*
iv. *GMP certificate of following manufacturer issued by respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided.*
    a. *Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.*
    b. *Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India*
    c. *Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia*

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

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

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

9. 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	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	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.

	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	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.	
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 of mentioned manufacturers need to be provided as per the Bio Study Rules, 2017.*	GMP certificates and the role of manufacturers are attached. **(Page 465-479/Corr.)**	*Provided all GMP certificate are issued by manufacturer itself. 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.*

19. Accordingly, the decision was communicated to applicant. Representative of PI provided GMP Certificate of **Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC,3207, Australia, issued by TGA, Australia.** And also informed that, the trial has two different sites, AKU, Kharadar is under inspection whereas, AKUH, Karachi is an approved site so, the trial may be considered for approval on approved site only.

20. Secretary CSC presented the case before the Committee.

Decision:

The CSC after detailed deliberation, discussion and considering the reply submitted by the applicant decided to:

i. *Approve the Phase-II Clinical Trial titled, "Can Esomeprazole Improve Outcomes in Women at High Risk of Pre-Eclampsia, A Phase II, Placebo-Controlled Randomized Multicenter Clinical Trial (The Espresso Study)" under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site:*
   a. *Aga Khan University, Karachi (CTS-0003)*

ii. *Approve the following quantities of IMPs to be imported:*

   a. *Aspirin 300mg (Solprin®) Tablets (235 Packs 92s)*
   b. *Esomeprazole/Placebo 40mg Tablets (35 Tablets/bottle) (410 Bottles)*

AGENDA ITEM-III

A PHASE 3 RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY TO EVAUATE THE EFFICACY AND SAFETY OF BEMNIFOSBUVIR IN HIGH RISK OUTPATIENTS WITH COVID-19. F.No.03-37/2023-CT(PS)

The case is an application dated 14-03-2023 from Dr. Nida Hussain (CNIC 42101-17301-8472273-2), Ziauddin University Hospital, Karachi, Clinical Trial Unit 4/B, Shahrah-e-Ghalib Rd, Block 6 Clifton, Karachi, 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 45036273490.

3. The trial is also enlisted on U.S National Trial Registry with identification number NCT05629962.

4. The details regarding **trial sponsor** & responsible party is as under: The anticipated cost of the project for 100 subjects is USD 397,120.

Atea Pharmaceuticals, Inc.
225 Franklin Street, Suite 2100
Boston, Massachusetts 02110, USA

5. **Brief Summary:**

The purpose of the study is to evaluate whether Bemnifosbuvir (BEM) is effective and safe in adults with COVID-19 who do not need to be in the hospital but who are at high risk for progression to severe disease. Eligible subjects will be randomly assigned (by chance) to receive BEM or matching placebo orally for 5 days. Co-administration of locally available standard of care (SOC) is allowed. The total duration of the study is 60 days.

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 45036273490
3	Investigator Brochure (s)	AT-527 Main Body Ed 09 (05 Aug 2022) (replaces edition no. 8)
4	Final protocol	AT-03A-017 Version 1.0 Final (08 Sep 2022)
5	Informed consent and participant information sheet (Urdu to English)	Version 1.0 (07Sep 2022) ---Master Informed Consent Form. Version 2.0 (21-12-2022) for Pakistan

<table>
<tr><td></td><td></td><td colspan="2">Main ICF_V1.0PAK2.0 (21Dec2022)</td></tr>
<tr><td>6</td><td>List of participating countries</td><td colspan="2">Argentina, Brazil, Canada, Colombia, Egypt, Germany, Ghana, India, Japan, Kenya, Latvia, Mexico, Morocco, Netherlands, Philippines, Romania, South Africa, Spain, Sweden, Tunisia, Turkey, United Kingdom, United States, Pakistan</td></tr>
<tr><td>7</td><td>Phase of trial.</td><td colspan="2">Phase – III
Duration of trial: Approximately one year from start of recruitment until close out. i.e. June 2023-July 2024.</td></tr>
<tr><td>8</td><td>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.</td><td colspan="2">Test Drug: 2600 tablets of Bemnifosbuvir (275mg) / Placebo.

Manufacturer of Drug Substance:
Topharman Shandong Co., Ltd
Address: 49 Wenshuibelu, Eonomic Development Zone, Anqiu City, Shandong Province, China 262123

Manufacturer of Drug Product (Active/Placebo):
Pace Life Sciences, LLC

Address: 600 Markley St, Norristown, PA 19401, USA

Active: Batch# 5181-01 (expiry Oct 2023)
Placebo: Batch# 5192-01 (expiry Oct 2023)

Country of Origin (Exporting Country) after Labelling

Rockford PCI Pharma Services
4536 Assembly Drive, Rockford, IL, 61109, US</td></tr>
<tr><td rowspan="5">9</td><td rowspan="5">Site of the trial</td><td>Site</td><td>PI</td></tr>
<tr><td>Ziauddin University Hospital, Karachi</td><td>Dr. Nida Hussain</td></tr>
<tr><td>Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad</td><td>Dr. Tanwir Khaliq</td></tr>
<tr><td>Avicenna Medical College & Hospital, Lahore</td><td>Dr. Waheed Ahmad</td></tr>
<tr><td>Al-Shifa Trust Eye Hospital</td><td>Dr. Ume Sughra</td></tr>
<tr><td rowspan="6">10</td><td rowspan="6">Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.</td><td>Site</td><td>IRB approval number/date</td></tr>
<tr><td>Ziauddin University Hospital, Karachi</td><td>23 Feb 2023</td></tr>
<tr><td>Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad</td><td>02 march 2023</td></tr>
<tr><td>Avicenna Medical College & Hospital, Lahore</td><td>IRB-36/01/23/AVC

24-01-2023</td></tr>
<tr><td>Al-Shifa Trust Eye Hospital</td><td>12-01-2023</td></tr>
<tr><td>The Aga Khan University Hospital(AKUH), Karachi</td><td>08 march 2023</td></tr>
</table>

11	Approval of National Bio-ethics Committee (NBC)	NBC approval reference letter No.4-87/COVID-133/23/1214 dated 14-Feb 2023 **For a period of Six Months**
12	CV's of the Investigators	CVs attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	COA and GMP certificate of Pace Life Sciences is attached. GMP certificate of Topharman Shandong Co., Ltd China is attached.
14	Pre-clinical/clinical safety studies	**Phase-I and Phase II studies are conducted for hepatitis C and now phase-III studies are planned for Covid-19.** **Phase-III for Covid-19 is approved in reference regulatory authorities.** **Reliance Mechanism in Regulatory processes, A DRAP's approach on Good Reliance Practices** reference regulatory authorities for matters related to registration of pharmaceutical & biological drugs, enlistment of alternative medicines & health products and **for approval of Clinical trials:**
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.	100 Subjects in Pakistan (20 for each Site) 1500 subjects globally.
19	Name of Monitors & Clinical Research Associate	**Karachi:** Sadia Hashmi & Bharti Kachela **Islamabad:** Asjid Ali Arshad, Naveed Akbar & Sidra Rashid **Lahore:** Mahir Ahmed, Hasina Sarwar, Saad Asadullah & Muhammad Asif Mahmood
20	Evidence of registration in country of origin.	N/A
21	Copy of registration letter (if registered in Pakistan)	N/A
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	Approximately one year from start of recruitment until close out. i.e. June 2023-July 2024.
23	Undertaking on Stamp paper	Attached.

Study Design:

Study Type	Interventional (Clinical Trial)
Estimated Enrollment :	1500 participants (Globally)…. 100 patients in Pakistan
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Care Provider, Investigator)
Primary Purpose:	Treatment

Condition:

- SARS CoV 2 Infection

- COVID-19

Intervention

- Drug: Bemnifosbuvir (BEM)
  BEM tablets administered orally every 12 hours (twice a day) for a total of 5 days
  Other Name: AT-527
- Drug: Placebo
  Placebo tablets administered orally every 12 hours (twice a day) for a total of 5 days

Primary and Secondary Objectives:

- **Proportion of subjects hospitalized due to COVID-19 or died due to any cause [Time Frame: Day 1 through Day 29]**
- Proportion of subjects who died due to any cause [Time Frame: Day 1 through Day 29; Day 1 through Day 60]
- Proportion of subjects with COVID-19-related complications [Time Frame: Day 1 through Day 29]
- Proportion of subjects with COVID-19-medically attended visits (hospitalization, emergency room (ER) visit, urgent care visit, physician's office visit, or telemedicine visit) or who died due to any cause [Time Frame: Day 1 through Day 29; Day 1 through Day 60]
- Proportion of subjects with COVID-19 symptom relapse [Time Frame: Day 1 through Day 29]
- Proportion of subjects with viral load rebound [Time Frame: Day 1 through Day 29]

Inclusion Criteria:

- Positive SARS-CoV-2 test conducted ≤ 5 days prior to randomization
- Mild or moderate COVID-19 with symptom onset ≤ 5 days before randomization and at least one COVID-19 related symptom present at time of screening
- Subject must be high risk, defined below:
  1. Age ≥80 years OR
  2. Age ≥65 years with one of the following: i) obesity (body mass index [BMI] ≥30 kg/m2) ii) diabetes mellitus iii) cardiovascular disease or hypertension iv) chronic lung disease requiring routine therapy OR
  3. Age ≥18 years with one of the following: i) Down syndrome, sickle cell disease, dementia, Parkinson's disease, or care home residents ii) One of the following immunocompromising conditions or immunosuppressive treatment: receiving chemotherapy or other therapies for cancer, hematologic malignancy, being within 2 years from receiving a hematopoietic stem cell or at any time following a solid organ transplant, human immunodeficiency virus (HIV) infection untreated or with CD4+ T lymphocyte count <350 cells per cubic millimeter within the past 6 months, combined primary immunodeficiency disorder, taking immunosuppressive medications
- Use of adequate contraception for females of childbearing potential

Exclusion Criteria:

- Severe or critical COVID-19 illness
- Admitted to a hospital within 90 days prior to randomization due to COVID-19
- Use of other investigational drugs within 30 days prior to planned dosing, or plans to enroll in another clinical trial of an investigational agent while participating in the present study
- Initiation or planned initiation of Remdesivir for treatment of the current SARS-CoV-2 infection
- Requirement of prohibited medications, including Hydroxychloroquine or amiodarone within 3 months prior to screening. Note: Subjects who had already initiated any COVID-19 drug with antiviral effects intended to treat symptomatic SARS-CoV-2 infection (≥ 24 hours prior to randomization) will be excluded. During screening (or within 24 hours prior to or after randomization), locally available COVID-19 drugs with antiviral effects (including but not limited to Paxlovid, Molnupiravir, favipiravir, monoclonal antibodies) will be permitted, as long as there are no concerns for drug interactions.
- Other known active viral or bacterial infection at the time of screening, such as influenza and respiratory syncytial virus (RSV). Note: This exclusion does not apply to subjects with stable chronic viral infections, such as chronic hepatitis C virus (HCV) or HIV providing other eligibility criteria are met.
- Receiving dialysis or have known moderate to severe renal impairment
- History of severe hepatic impairment (Child-Pugh Class C)
- Known allergy or hypersensitivity to components of study drug.

DRAP QUERIES

Protocol Number: AT-03A-017

Title: "A **Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Bemnifosbuvir in High-Risk Outpatients with COVID-19**."

<table>
<tr><th>Sr.</th><th>DRAP Comments</th><th>PI's Response</th></tr>
<tr><td>1</td><td>GMP Certificates for all manufacturers involved in different operations need to be provided along with their relation in the trial medicine. (Relation between M/s Topharman Shandong Co., Ltd., (Manufacturer of Drug Substance), China, M/s Pace Life Sciences, LLC, USA & M/s Pace Life Sciences, LLC, USA (Packaging site) need to be elaborated.)</td><td>The Sponsor hereby provides the GMP certificate of Topharman and GMP audit by QP for Pace Life Sciences and clarification related to the relationship between the manufacturers. The Sponsor separately contracts with Topharman Shandong Co., Ltd. for manufacture of drug substance, and Pace Life Sciences, LLC, USA for manufacture and packaging of drug product. After Topharman Shandong Co., Ltd completes manufacture of drug substance, the Sponsor provides Topharman Shandong Co., Ltd authorization to ship the drug substance to Pace Life Sciences, LLC, USA for use in manufacture of Atea drug product and for packaging of tablets. Topharman Shandong Co., Ltd. and Pace Life Sciences, LLC, USA have no direct relationship or interactions.</td></tr>
<tr><td>2</td><td>Both trial drugs (Placebo/Active) have short shelf life (only Seven Months). So, it needs clarification as trial ends in December-2023 or in July 2024 & medicine will expire in October-2023.</td><td>As informed by the study team, the trial ends in December-2023. Please find attached the document with the proposed duration of the trial.
The Sponsor hereby would like to provide clarification regarding the Shelf-life of the trial drugs (Active and Placebo).
As we indicated in our IMPD, 18 M expiry has been assigned to the trial drugs based on 6 M real time stability data. However, we are in the process of extending the shelf-life to 21 Months based on 9 M real time data and subsequently to 24 months based on 12M real time data and up to 36months.
We have included batch information of two active lots (5059-12 and 5181-01) and two placebo lots (5059-01 and 5192-01) in the IMPD. For the clinical study in Pakistan, 5181-01 (active) and 5192-01 (placebo) will be used and will have expiry dating of Jan 2024 (based on 18M shelf-life). Furthermore, these expiry dates on these lots will be extended as more data becomes available. The lot specific expiry dating schedule is shown in the table below.
<table>
<tr><th rowspan="2">Lot</th><th>18M expiry</th><th>21M expiry</th><th>24M expiry</th><th>30M expiry</th><th>36M expiry</th></tr>
<tr><th>MM-YY</th><th>MM-YY</th><th>MM-YY</th><th>MM-YY</th><th>MM-YY</th></tr>
<tr><td>5059-12</td><td>Sep-23</td><td>Dec-23</td><td>Mar-24</td><td>Sep-24</td><td>Mar-25</td></tr>
<tr><td>5059-01</td><td>Sep-23</td><td>Dec-23</td><td>Mar-24</td><td>Sep-24</td><td>Mar-25</td></tr>
<tr><td>5181-01</td><td>Jan-24</td><td>Apr-24</td><td>Jul-24</td><td>Jan-25</td><td>July-25</td></tr>
<tr><td>5192-01</td><td>Jan-24</td><td>Apr-24</td><td>Jul-24</td><td>Jan-25</td><td>July-25</td></tr>
</table></td></tr>
<tr><td>3</td><td>IRB composition of Ziauddin Hospital (Page 297) & Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad (Page 292) are not as per the Bio-Study Rules, 2017 & ICH-GCP Guidelines. AKUH IRB/ERC Composition is not provided.</td><td>Please find attached IRB Composition of AKU and Ziauddin Hospital.

Please note that in the Ziauddin Hospital member list, Ms. Anika Khan is the non-scientific and external member.</td></tr>
<tr><td>4</td><td>Approval of other NRAs as claimed needs to be attached.</td><td>Please find attached country approvals as per NRA list.</td></tr>
<tr><td>5</td><td>Pre-clinical/clinical safety studies need to be elaborated along with Phase-I & Phase-II trial results if any publications are available need to be shared.</td><td>As for the pre-clinical and clinical safety studies, these are all covered in the IB. Please also find attached the literature reference document and clarification letter provided by the sponsor.</td></tr>
<tr><td>6.</td><td>Duration of trial in form mentioned as June 2023 – Dec- 2023 (Page</td><td>The duration of the trial is approximately six months from start of recruitment until close-out i.e., June 2023 – Dec 2023.</td></tr>
</table>

	04), whereas at other places in document (Pages 233 & 412) mention as June 2023 – July 2024 (One year/12 Months), it should be clarified.	

March 30, 2023

Subject: Development of Bemnifosbuvir
Protocol#: AT-03A-017
Protocol title: A Phase 3 Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Bemnifosbuvir in High-Risk Outpatients with COVID-19
Sponsor: Atea Pharmaceuticals, Inc.

To Whom It May Concern:

Prior to 2020, Bemnifosbuvir (AT-527) was **initially being developed by Atea Pharmaceuticals, Inc. (Atea) for the treatment of Hepatitis C viral infection**. With the advent of the worldwide COVID-19 pandemic, and within vitro data indicating promising antiviral efficacy against SARS-CoV-2, Atea initiated a development program for COVID-19. To date, over 600 human subjects have been exposed to BEM across both the COVID-19 and HCV development programs. Of these, over 350 human subjects have received BEM at or above the selected dose and duration for the proposed Phase 3 study.
Specifically, for COVID-19, a Phase 3 study (CV43043, MORNINGSKY) was initiated in 2021. The study was terminated prematurely due to program and operational decisions, with no safety concerns. This study was a randomized, placebo-controlled study in **non-hospitalized adult** and adolescent patients with mild or moderate COVID-19 who were at high risk or standard risk for disease progression. The study also allowed vaccinated patients to be enrolled. Patients were randomized (2:1) to receive 550 mg BEM or placebo BID for 5 days. **The primary endpoint was time to alleviation/improvement of COVID-19 symptoms**. Secondary endpoints included hospitalization, all-cause mortality and change in viral load. At the time of discontinuation, 216 patients had been randomized (2:1; active: placebo), with 207 patients included in the efficacy evaluable population. The study enrolled a broad outpatient population, with 47% who were high risk, 28% who were vaccinated, and 56% who were seropositive at baseline. **Because the study was prematurely discontinued, no formal statistical comparisons were made and results are presented descriptively**. **Although the primary endpoint of symptoms alleviation or improvement was not met, a lower proportion of patients required hospitalization for COVID-19 (secondary endpoint**) in the BEM arm (2.9%; 4/137 patients) compared to the placebo arm (10%; 7/70 patients). This represents a **71% reduction in hospitalization in patients** who received BEM. This clinical observation favoring the BEM arm was consistent for the clinical outcome secondary efficacy endpoints, including_COVID-19 related medically attended visits (10.2% vs 14.3%; BEM vs placebo), COVID-19 related complications (4.4% vs 10.0%) and post-treatment infections (9.5% vs 14.3%). There were no deaths in the study. There was no meaningful difference in the change from baseline in viral load between the BEM arm and the placebo arm. In addition, the safety and tolerability of the 550 mg BID dose was generally comparable to placebo. There were no drug-related serious adverse events (SAEs) reported, and proportions of patients with adverse events (AEs) leading to study drug discontinuation were low (2.8% in the BEM arm vs 7.0% in the placebo arm). Overall, gastrointestinal (GI) AEs were 11.3% in the BEM arm vs. 9.9% in the placebo arm. There were more drug-related GI AEs (nausea, diarrhea, abdominal discomfort/pain) in the BEM arm (9.2%) compared to placebo (1.4%), but all were low grade (mild/moderate) and none resulted in treatment discontinuation. There was no reported vomiting in the BEM arm.

Although CV43043 was prematurely discontinued and did not meet the primary endpoint of symptom alleviation, the positive signal observed in hospitalization/deaths is the most clinically important and relevant finding to support the new proposed Phase 3 AT-03A-017 study.
Two Phase 2 COVID-19 treatment studies have also been conducted, one in an outpatient population (WV43042, MOONSONG) and one in hospitalized patients with moderate COVID-19 (AT-03A-001). The results of these trials are described in the protocol and investigator's brochure. **WV43042 was a Phase 2 virology dose-ranging study designed to evaluate the antiviral activity, safety, PK and efficacy of BEM in non-hospitalized adult patients with mild or moderate Covid-19 who were at high risk or standard risk. The doses evaluated were 550 mg BD and 1100 mg BD for 5 days. The study did not meet its primary virology endpoint of reduction in the amount of SARS-Cov-2 virus. Nevertheless, there were positive virology trends observed in exploratory subgroups of patients at high risk. AT-03A-001 was a prematurely discontinued Phase 2 study designed to evaluate the safety, antiviral activity and efficacy of BEM in high risk adult hospitalized patients with moderate Covid-19. Part-A of the study evaluated a dose of 550 mg BID for 5 days. Part B was intended to evaluate a dose of 1100 mg BID for 5 days. This study was also prematurely discontinued due to the changing Covid-19 landscape as management and standard of care for hospitalized Covid-19 patients had adapted, making continued enrollment in a placebo controlled trial no longer feasible in a hospitalized population.**

Finally, a full Phase 1 clinical pharmacology program has been conducted for Bemnifosbuvir, supporting both the COVID-19 and HCV programs.
The Sponsor considers that the development to date provides sufficient justification to initiate the AT-03A-017 trial.

07. Secretary CSC presented the case before the Committee.

Decision:

The CSC after detailed deliberation, discussion and considering the reply submitted by the applicant decided to:

i. Approve the Phase-III Clinical Trial titled, "A Phase 3 Randomized, Double Blind, Placebo-Controlled Study to Evaluate the Efficacy and Safety of Bemnifosbuvir in High Risk Outpatients with COVID-19" under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site(s):

a. Ziauddin University Hospital, Karachi (CTS-0086)
b. Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad (CTS-0003)
c. Avicenna Medical College & Hospital, Lahore (CTS-0052)
d. Al-Shifa Trust Eye Hospital, Rawalpindi (CTS-0044)
e. Aga Khan University Hospital(AKUH), Karachi (CTS-0003)

ii. Direct the PI to submit interim results at 07th, 14th and 28th days for every 25 Subjects, after endorsement form Data Safety Monitoring Board/Committee.

iii. Approve the following quantities of IMPs to be imported:

***Test Drug:** 2600 tablets of Bemnifosbuvir (275mg) / Placebo.*

Manufacturer of Drug Product (Active/Placebo):
Pace Life Sciences, LLC, Address: 600 Markley St, Norristown, PA 19401, USA.

Active: Batch# 5181-01 (expiry Oct 2023)
Placebo: Batch# 5192-01 (expiry Oct 2023)

Country of Origin (Exporting Country) after Labelling
Rockford PCI Pharma Services, 4536 Assembly Drive, Rockford, IL, 61109, US

AGENDA ITEM IV:

APPLICATION FOR PPROVAL OF CLINICAL TRIAL TITLED, "A PHASE II, RANDOMIZED, OBSERVER-BLINDED, PLACEBO CONTROLLED TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF HECOLIN® IN HEALTHY PREGNANT WOMEN BETWEEN GESTATIONAL AGE 14-34 WEEKS AND NON-PREGNANT WOMEN OF 16-45 YEARS OLD" FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-35/2023-DD (PS)

Dr. Imran Nisar, CNIC number: 42301-9043152-5, Principal Investigator (PI) & Assistant Professor, Department of Pediatrics and Child Health, Aga Khan University Hospital, Karachi, dated 30th March, 2023, wherein request has been made for approval of subject 'Clinical Trial' on prescribed Form-II, along with a fee of Rs. 200,000/- deposited vide challan no. 1190149752, dated 27th March, 2023. The trial is also submitted to enlisted on Clinicaltrial.gov Trial Registry dated 19-03-2023 with the trial name "A Phase II, Randomized, Observer-blinded, Placebo Controlled Trial to Evaluate the Safety and Immunogenicity of Hecolin® in Healthy Pregnant Women Between Gestational Age 14-34 Weeks and Non-Pregnant Women of 16-45 Years Old."

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

i. Sponsor: International Vaccine Institute, Korea
ii. Collaborators: Open Philanthropy
Bill and Melinda Gates Foundation
Thrasher Research Fund
iii. Number of subjects to be recruited: 2,358 participants approx.

iv. Anticipated cost of the project: PKR 23,595,220/-

3. Purpose of trial:

Hepatitis E virus (HEV) is the leading cause of acute viral hepatitis in the world, with a disproportionately high burden of disease and death among pregnant women in developing regions. There are approximately 20 million infections, 70,000 deaths, and 3,000 stillbirths each year. Hepatitis E virus is prevalent in Pakistan where the clinical trial will be conducted. The hepatitis E is widespread and affects most of the population in the country. HEV during pregnancy causes substantial maternal morbidity and mortality in South Asia and Africa, largely attributed to genotype 1 and 2. This increase in morbidity and mortality has not been observed with genotype 3, and 4 infections. The case-fatality rates for genotype 1 vary from 10 to 40% depending on the study site and design. With over 35 million births each year in South Asia, HEV may contribute to as many as 60,000 preventable maternal or fetal deaths each year. Studies from Bangladesh have estimated that approximately 10% of all maternal mortality could be due to HEV, which would suggest over 10,000 deaths per year in South Asia from HEV. However, the lack of public health surveillance systems and diagnostic tests make it difficult to measure the burden of HEV during pregnancy in endemic areas. There is strong evidence that Hecolin® is safe and efficacious in preventing hepatitis E associated disease in normal healthy adults as described in the clinical data section below. There is an ongoing study in Bangladesh (NCT02759991) to define the effectiveness of Hecolin® administered to women of childbearing age in preventing HEV related morbidity including among women who subsequently become pregnant.

The primary goal of this clinical trial is to establish the safety and immunogenicity of Hecolin® during pregnancy. As secondary and exploratory objectives, infant immune response through passive immunization of infants achieved through transplacental transfer of maternal IgG antibodies from the pregnant mother who has received Hecolin® in the second or third trimester will be evaluated. As HEV causes substantial maternal morbidity and mortality among pregnant women in South Asia and Africa, the study will evaluate the safety and immunogenicity of Hecolin with a 2-dose regimen administered during pregnancy, followed by completion of the third dose after delivery. Considering the high short-term efficacy demonstrated after 2 doses in the phase 3 trial, and the practical limitations of completing a 3 dose regimen during pregnancy, this schedule offers the best balance of potential risk and benefit. Demonstration of safety and immunogenicity of the vaccine in women already pregnant will enable inclusion of pregnant women in vaccine deployment during outbreaks or other high-risk settings.

4. Study design & details:

Study type	Investigational (Clinical Trial)
Estimated Enrollment :	2,358 participants.
Allocation:	Randomized, Blinded
Intervention Model:	Parallel Assignment
Masking:	Triple (Participant, Investigator, Outcomes Assessor)
Primary Purpose:	Prevention
Duration :	24-months

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

Sr.#	Proposed Site(s) of CT	Investigator
1.	Aga Khan University Hospital, Karachi.	Dr. Imran Nisar Principal Investigator (PI) & Assistant Professor, Department of Pediatrics and Child Health, Aga Khan University, Karachi

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

i. Aga Khan University Hospital, Karachi (Sending Party)
ii. International Vaccine Institute SNU Research Park, 1 Gwanak-ro, Gwanak-gu, Seoul, 08826 Republic of Korea (Receiving Party)
iii. DRK Pharma Solutions, 1st Floor, Building No. 1, The Enterprise, 15 km, Multan Road, Lahore 53800, Pakistan. **(L-CRO).**

7. Identity of investigational Vaccine: -

The investigational vaccine is Hecolin® (Recombinant Hepatitis E Vaccine (Escherichia coli)): the placebo is normal saline (Sterile 0.9% sodium chloride). **Both were provided by International Vaccine Institute** Details of IMPs are as follows:

Item	**Investigational Vaccine**	**Placebo**
Drug name	Hecolin® (Recombinant Hepatitis E Vaccine (Escherichia coli))	Normal Saline
Strength	30μg/dose, 0.5ml/Vial	0.5 ml/Vial
Batch No	A202211014	
Description	Milky-white suspension	Clear liquid
Storage & Transportation	+2 to +8°C	
Shelf Life	36 months (tentatively)	
Manufacturer/Supplier	Xiamen Innovax Biotech Co., Ltd.	
Route of administration	Intramuscular injection into the lateral deltoid muscle.	
Immunization Procedure	Intramuscular injection on 0, 1 and 6 month, respectively.	

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

Sr.#.	**Document**	**Remarks**
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs. 200,000/- deposited vide challan no. 1190149752, dated 27th March, 2023
3	Investigator Brochure (s)	Hecoline® - Recombinant Hepatitis E vaccine (E.coli), Version 4, Dated: August, 2022 and Investigator's Brochure for Phase I clinical Trial of recombinant (E.coli) Hepatitis E Vaccine Hecoline version 3.0 are attached.
4	Final protocol	IVI_Hecolin_P001_Protocol_V2.0, Dated: 03 February, 2023 is attached.
5	Informed consent and participant information sheet (Urdu to English)	IVI_Hecolin_P001_Pakistan Main ICF_V3.0, 3.0, Dated: 07 March, 2023 is attached.
6	List of participating countries	Pakistan only.
7	Phase of trial.	Phase – II
8	Quantity of drug / trial material to be imported.	8,000
9	Site of the trial	Aga Khan University Hospital, Karachi
10	Institutional Review Board (IRB) approval of site with complete composition of committee i.e. names and designation of members.	IRB/ERC approval of **Aga Khan University Hospital**, **Karachi** dated 13th March, 2023 for a period of one year is attached.
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter No. **Ref: No.4-87/NBC-910/22/1483**, dated 22nd March, 2023 for a period of **one year** is attached.
12	CV's of the Investigators	CVs of PI Dr. Imran Nisar is attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP statement GMP Certificate(s) issued by Fujian Medical Products Administration and Pharmaceutical Production Licence Pharmaceutical Product approval in china is attached.
14	Pre-clinical/clinical safety studies	Attached. Attached (IB Page 13-30)

15	Summary of Protocol	IVI_Hecolin_P001_Protocol_V2.0_Protocol Summary, Dated: 03 February, 2023 is attached.
16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	2358
19	Name of Monitors & Clinical Research Associate	Talha Javed Zainab Shahid Nasir Abbas Shiza Ashraf Roha Badar Fizza Khalid
20	Evidence of registration in country of origin.	Attached.
21	Copy of registration letter (if registered in Pakistan)	Attached.
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	24 Months
23	Undertaking on Stamp paper	Attached.

09. Secretary CSC presented the case before the Committee.

Decision:

The CSC after detailed deliberation & discussion decided to:

i. Approve the Phase-III Clinical Trial titled, "A Phase II, Randomized, Observer-Blinded, Placebo Controlled Trial to Evaluate the Safety and Immunogenicity of Hecolin® in Healthy Pregnant Women between Gestational age 14-34 Weeks and Non-Pregnant Women of 16-45 Years Old" under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site:

a. Aga Khan University Hospital(AKUH), Karachi

ii. Approve the following quantities of IMPs to be imported:

Item	***Investigational Vaccine***
Drug name	*Hecolin® (Recombinant Hepatitis E Vaccine (Escherichia coli))*
Strength	*30µg/dose, 0.5ml/Vial*
Batch No	*A202211014*
Description	*Milky-white suspension*
Storage & Transportation	*+2 to +8°C*
Shelf Life	*36 months (tentatively)*
Manufacturer/Supplier	*Xiamen Innovax Biotech Co., Ltd.*
Route of administration	*Intramuscular injection into the lateral deltoid muscle.*
Immunization Procedure	*Intramuscular injection on 0, 1 and 6 month, respectively.*
Quantity to be imported	*8,000 Injections*

AGENDA ITEM V:

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 20mg/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 20mg/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 day 7,14,28 and 90, if 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. Way Forward

- *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.

7. Discussion:

During the finalization of the minutes, Mr. Waqas Latif raised queries regarding the non-justified increase in IMPs in lieu of participants and submitted the following remarks through email:
For AGENDA ITEM XV, the justification given by the PI for the revision of the quantities of IMPs is not correlated with the increase in sample size. Although there is a 50% increase in sample size, the medicine quantity has increased by 350%. Therefore, we need to verify the quantity of medicine. Therefore, you have to address the concerns raised in agenda item XV before proceeding.
Dr. Saeed Ahmed is also in favor of the questions raised by Mr. Waqas Latif. The Chairman CSC after the discussion decided to defer the case for clarification and after the submission of justification by PI, the matter will be placed again before CSC.

8. *Decision: -*

*The CSC after detailed discussion and deliberation decided to defer the case for further review /and clarification from PI regarding the increase in trial sample size (i.e. **375** Subjects to **560** Subjects) and justification for the increase in IMPs in respect of the increased sample size.*

9. Accordingly, CSC decision was communicated on 21st March, 2023. Reply from Prof. Dr. Farah Naz Qamar, Associate Professor, Department of Pediatrics & Child Health, Aga Khan University Hospital, Karachi received on 27th March 2023.

10. PI submitted clarification regarding increase in trial sample size (i.e. 375 Subjects to 560 Subjects) and justification for the increase in IMPs in respect of the increased sample size and is reproduced as under;

The quantity of the drugs has been calculated based on weight estimation because it is difficult to predict the weight of the patient and quantity of drugs to be dispensed prior to randomization. Therefore, the quantity of the drugs is inflated up to the maximum dosage requirement of the patient. The study sample size is 560 however, the quantity is tripled to cover for the dosage compliance, emergency dose (drug loses) and blinded nature of the interventional drug. The record of IMP dispensed, unused and returns is maintained in the drug accountability log at each site as well as at CTU. The drug accountability log will be submitted to DRAP for the scrutiny at the end of the trial. The sample of accountability log and drug dosing table has been attached as an annexure I & II for your record and future reference.

The aim is to enroll 560 participants with a distribution of 460 children (<16 years) and 104 adults (>16 years). Further the cut-off for weight is taken as below 21 kg and above 21 kg, and we assume equal distribution of participants in each group of 230 patients in pediatrics population. Therefore, the quantity of IMP has been distributed accordingly to cover the desired sample size with 20% inflation. The justification each IMP quantity is given in table below.

- *Azithromycin dosage form (tablet 250 & 500mg and syrup) is dispensed based on weight of the patient and daily dose requirement in mgs. The convenience of the patient is taken into consideration while dispensing the drugs. In our experience of enrolling 66 patients, the younger patients prefer the syrup formulation but in some instances the tablet form is preferred, similarly the choice of the adults for syrup or tablet is variable. Therefore, we have accounted for the availability of both tablet and syrup form in equal quantity for the entire sample size of the study. The detailed calculation of the dosage and quantity is provided in the footnote of the table 1.*
- *Cefixime is received in sealed in envelopes from the funding agency. Each envelop contains maximum number of tablets which includes both 100mg (5 strips) and 400mg (2 strips). Therefore, they are dispensed as the dosage requirement of the patient and unused tablets are maintained in the randomization envelop and returned to CTU along with drug returns. The randomization packet and its contents are shown in picture and detail quantity in footnote of table 1.*

Cefixime/Placebo randomization

Name of IMP	Dose per participant for 7 days (tablets/susp ml)	Additional dose to cover the losses (tablet/susp ml)	Total quantity of tablets/suspension per patient	Number of strips/bottles

[1]*Azithromycin 250 mg*	*28 tablets*	*6 tablets*	*34 tablets*	*909 strips*
[2]*Azithromycin 500 mg*	*14 tablets*	*4 tablets*	*18 tablets*	*2160 strips*
[3]*Azithromycin 15 ml suspension*	*157.5 ml*	*45 ml*	*202.5 ml*	*280 bottles*
[3]*Azithromycin 30 ml suspension*	*157.5 ml*	*45 ml*	*202.5 ml*	*1200 bottles*
[4]*Cefixime 100 mg DT*	*42 tablets*	*6 tablets*	*48 tablets*	*2400 strips*
[5]*Cefixime 400 mg*	*14 tablets*	*2 tablets*	*16 tablets*	*1200 strips*

Table 1 Detail description of IMP according to sample size

[1]Each strip of Azithromycin 250mg contains 6 tablets, the maximum dose dispensed 1 gram per day for 7 days (4x7=28 tablets of 250 mg per patient), additional 6 tablets of 250 mg per patient to cover the loses. The maximum number of tablets i.e. 34 tablets of 250 mg azithromycin are calculated for an approximate sample size of 200 (34x160=5440 tablets, 909 strips)

[2]Each strip of Azithromycin 500mg contains 3 tablets, the maximum dose dispensed 1 gram per day for 7 days (2x7=14 tablets of 500 mg per patient), additional 4 tablets of 500 mg per patient to cover the loses. The maximum number of tablets i.e. 18 tablets of 500 mg azithromycin are calculated for an approximate sample size of 360 (18x360=6480 tablets, 2160 strips)

[3]Each bottle contain 30ml or 15ml volume, the maximum dose dispensed per day is 900mg (22.5ml) for 7 days (22.5mlx7= 157.5ml, 7 bottles of 30ml per patient) including doses to cover loses. The maximum number of bottles required are 7 with 30ml volume 7 calculated for an approximate sample size of 172 patients. As for the 15ml volume bottle the dose regimen remains the same and the quantity of bottles is calculated for approximate sample size of 20 patients.

[4]Each pediatric randomized packet of Cefixime/placebo contains 5 strips of 100mg DT and 2 strips of 400mg (each strip of either 100mg or 400mg contains 10 tablets). The maximum dose dispensed 600mg/day in two divided doses (6x7=42 tablets of 100mg per patient) OR 400mg per patient as per the convenience of the patient, additional 6 tablets of 100mg per patient to cover the loses. The maximum number of tablets i.e. 48 tablets of 100 mg cefixime/placebo are calculated for an approximate sample size of 500 (48x500=24000 tablets, 2400 strips).

[5]Each adult randomized packet of Cefixime/placebo contains 2 strips (each strip contains 10 tablets) of 400mg. The maximum dose dispensed 800mg/day in two divided doses (2x7=14 tablets of 400mg per patient), additional 2 tablets of 400mg per patient as an emergency dose. The maximum number of tablets i.e. 16 tablets of 400 mg cefixime/placebo are calculated for an approximate sample size of 600 (20x600=12000 tablets, 1200 strips). The sample size for 400mg cefixime/placebo exceed the actual study sample size because each pediatric packet contains 2 strips of to cover sample size of 500 patients, the remaining sample size is for 100 adult patients.

We applied for the amendment in the month of January 2022, meanwhile the medicines in the current shipment expired in the month of November 2022. Therefore, the amendment is requested on the revised quantity which includes the revised quantity of medicines excluding the amount that was consumed till November 2022, the quantity mentioned for final approval is mentioned in the last column.

SN	***Medicine name***	***Revised quantity for entire study duration (sample size 560)***	***Total quantity approved in initial DRAP application***	***Total quantity received in first & second shipment***	***Amount consumed for the enrollment of 66 patients***	***IMP Expired in Nov 2022***	***Final approval requested on this quantity***
1	*[1]Azithromycin 250 mg*	*909 strips*	*200 strips*	*200 strips*	*06 strips*	*194 strips*	*903 strips*
2	*[2]Azithromycin 500 mg*	*2160 strips*	*416 strips*	*414 strips*	*00 strip*	*414 strips*	*2160 strips*
3	*[3]Azithromycin 15 ml*	*280 bottles*	*100 bottles*	*100 bottles*	*45 bottles*	*55 bottles*	*235 bottles*
4	*[3]Azithromycin 30 ml*	*1200 bottles*	*600 bottles*	*600 bottles*	*175 bottles*	*425 bottles*	*1025 bottles*
5	*[4]Cefixime 100 mg DT*	*2400 strips*	*2,300 strips*	*1625 Strips*	*325 strips*	*1300 strips*	*2075 strips*
6	*[5]Cefixime 400 mg*	*1200 strips*	*668 strips*	*668 Strips*	*130 strips*	*538 strips*	*1070 strips*

Table 2 The quantity of IMP requested for an approval

09. Secretary CSC presented the case before the Committee.

Decision:

The CSC after detailed deliberation, discussion and considering the reply submitted by the applicant decided to approve the following additional quantities of IMPs for Clinical Trial titled, "Azithromycin & Cefixime Treatment of Typhoid in South Asia Trial (ACT-South Asia Trial)", due to amendment in trial protocol version 1.3 to 1.4 & an increase in trial sample size (i.e. 375 Subjects to 560 Subjects):

SN	Medicine name	Revised quantity for entire study duration (sample size 560)	Total quantity approved in initial DRAP application	Total quantity received in first & second shipment	Amount consumed for the enrollment of 66 patients	IMP Expired in Nov 2022	Final approval requested on this quantity
1	[1]Azithromycin 250 mg	909 strips	200 strips	200 strips	06 strips	194 strips	903 strips
2	[2]Azithromycin 500 mg	2160 strips	416 strips	414 strips	00 strip	414 strips	2160 strips
3	[3]Azithromycin 15 ml	280 bottles	100 bottles	100 bottles	45 bottles	55 bottles	235 bottles
4	[3]Azithromycin 30 ml	1200 bottles	600 bottles	600 bottles	175 bottles	425 bottles	1025 bottles
5	[4]Cefixime 100 mg DT	2400 strips	2,300 strips	1625 Strips	325 strips	1300 strips	2075 strips
6	[5]Cefixime 400 mg	1200 strips	668 strips	668 Strips	130 strips	538 strips	1070 strips

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AGENDA ITEM VI:

APPLICATION FOR PROTOCOL AMENDMENT FROM 2.0 TO 3.0 OF AN ALREADY APPROVED CLINICAL TRIAL TITLED, "A RANDOMIZED, DOUBLE-MASKED, PARALLEL-GROUP, MULTICENTER CLINICAL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF AVT06 COMPARED WITH EU-EYLEA® IN SUBJECTS WITH NEOVASCULAR (WET) AGE-RELATED MACULAR DEGENERATION - ALVOEYE STUDY". F.NO.03-12/2022-CT(PS)

It is submitted that, subject application was approved by the CSC & registration letter CT-0043 was issued on 02nd December 2022. Dr. M.A. Rehman Siddiqui PI of the trial submitted a request for amendment in already approved Clinical Trial Protocol version 2.0 to 3.0. Applicant submitted prescribed fee of Rs.25000/- vide challan number 57784549079, dated 29th March, 2023.

2. Summary of changes are attached as **Annexure-I**

3. Submitted for consideration of CSC, please.

4. Secretary CSC presented the case before the Committee.

Decision: -

*The CSC after discussion and deliberation decided to approve the protocol amendment from version 2.0 to 3.0 of already approved Clinical Trial Titled, "A Randomized, Double-Masked, Parallel-Group, Multicenter Clinical Study to Evaluate the Efficacy and Safety of AVT06 Compared with EU-Eylea® in Subjects with Neovascular (WET) Age-Related Macular Degeneration - ALVOEYE Study", under the Bio-Study Rules, 2017. (Summary of changes attached **Annex-I**)*

AGENDA ITEM VII:

APPLICATION FOR EXTENSION IN ALREADY APPROVED CLINICAL TRIAL TITLED, "A PHASE III, RANDOMIZED, OBSERVER-BLIND, MULTICENTER STUDY TO EVALUATE THE EFFICACY, IMMUNOGENICITY AND SAFETY OF SEQIRUS' CELL-BASED QUADRIVALENT SUBUNIT INFLUENZA VIRUS VACCINE (QIVC) COMPARED TO A NON-INFLUENZA VACCINE WHEN ADMINISTRATED IN HEALTHY SUBJECTS AGED 6 MONTHS THROUGH 47 MONTHS - SEQIRUS STUDY" F.No.03-11/2022-DD (PS)

Application received from Dr. Fatima Mir, PI & Associate Professor, Department of Pediatrics and Child Health, The Aga Khan University Hospital, Karachi, Pakistan, Stadium Road, Karachi dated 30th March, 2023. Wherein request has been made for extension in already approved Clinical Trial (CT-0039) for another one year. Prescribed processing fee of Rs. 25000/- paid vide challan number 145114692, dated 07th April, 2023.

02. Application reproduced as under:

Subject: DRAP renewal for the study title "A Phase III, Randomized, Observer-blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus' Cell Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine when Administered in Healthy Subjects aged 6 Months through 47 Months" Ref No: F.No.03-11/2022-DD (PS)"

Dear Chair,

I am writing with reference to your approval letter for the study title "A Phase III, Randomized, Observer-blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus' Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine when Administered in Healthy Subjects aged 6 Months through 47 Months" Ref No: F.No.03-1112022-DD (PS)" dated 21st Oct 2022 to request one-year extension on behalf of Dr. Fatima Mir (PI of the study).

Recruitment target of 750 subjects were set by Seqirus for Pakistan, out of which Pakistan has enrolled 560 subjects. We are expecting last patient last visit in Jul 2023.
The study has received the ERC and NBC approvals:

- *ERC approval: 02nd Aug 2022.*
- *NBC approval: 25th Aug 2022.*

03. Applicant submitted following documents:

i. Copy of Registration Letter (CT-0039)
ii. Drug Import Licence (K-1415526089762)
iii. Study Progress Report (Nov-2022 to Jan-2023)
iv. AKUH IRB/ERC approval, dated 02nd August 2022 (for a period of one year)
v. NBC Approval dated 25th August 2022 (for a period of one year)
vi. Prescribed fee challan.

04. Secretary CSC presented the case before the Committee.

Submitted for consideration of CSC, please.

Decision:

The CSC after discussion and deliberation decided to approve extension in the trial duration of Clinical Trial titled, "A Phase III, Randomized, Observer-Blind, Multicenter Study to Evaluate the Efficacy, Immunogenicity and Safety of Seqirus' Cell-Based Quadrivalent Subunit Influenza Virus Vaccine (QIVc) Compared to a Non-Influenza Vaccine when administrated in Healthy Subjects aged 6 months through 47 months - SEQIRUS Study" as approved by the IRB & NBC (w.e.f. 02nd August 2022 to 01st August 2023.)

AGENDA ITEM VIII:

CHANGE OF SOURCE OF ONE OF THE IMP IN CLINICAL TRIAL TITLED, "FINDING TREATMENTS FOR COVID-19: A PHASE 2 MULTI-CENTRE ADAPTIVE PLATFORM TRIAL TO ASSESS ANTIVIRAL PHARMACODYNAMICS IN EARLY SYMPTOMATIC COVID-19 (PLATCOV)". F.NO.03-18/2022-CT(PS)

It is submitted that, subject application was approved by the CSC & registration letter CT-0047 was issued on 22nd February 2023. Dr. Muhammad Asim Baig PI of the trial submitted a request that, the sponsor, the University of Oxford, has changed the manufacturer of the Nirmatrelvir/Ritonavir used in the study in Pakistan from Eskayef's Paxovir to Pfizer's PAXLOVID™. Applicant submitted a fee of Rs.7500/- vide challan number 0318944601.

2. Application for change of IMP source is reproduced as under:

Re: Finding treatments for COVID-19: A phase 2 multi-centre adaptive platform trial to assess antiviral pharmacodynamics in early symptomatic COVID-19 (PLATCOV)

Dear Drug and Regulatory Authority of Pakistan,

On behalf of the sponsor, the University of Oxford, we request a change of manufacturer of the Nirmatrelvir/ritonavir used in the study in Pakistan from Eskayef's Paxovir to Pfizer's PAXLOVID™.

Due to earlier difficulties procuring the original Pfizer PAXLOVID™ outside of Thailand (in Thailand it was donated by the Ministry of Public Health for use in the study within Thailand), we had requested to use of Paxovir, the Eskayef generic in the study. We have now secured Pfizer's PAXLOVID™ for use in Pakistan, which is the original version, and the one we are using in Thailand, Lao PDR and Brazil. This medication has US FDA EUA. Using Pfizer's PAXLOVID™ in all sites, allows for greater comparability and confidence in the results of the study.

Thank you for your support of the study.

3. In view of above, it is proposed that, applicant may be asked to submit prescribed processing fee of Rs. 25000/- and the matter regarding change of IMP source may be considered by the Clinical Studies Committee, please.

4. Secretary CSC presented the case before the Committee.

Decision:

The CSC after discussion and deliberation decided to approve the use of Eskayef's Paxovir to Pfizer's PAXLOVID™ in already approved Clinical Trial titled, "Finding Treatments for COVID-19: A Phase 2 Multi-Centre Adaptive Platform Trial to Assess Antiviral Pharmacodynamics in Early Symptomatic COVID-19 (PLATCOV)", under the Bio-Study Rules, 2017.

AGENDA ITEM IX:

APPLICATION FOR APPROVAL TO ACT AS CRO AT M/S CONTINUUM RESEARCH CENTER, WAH CANTT. F. No.15-20/2022-CRO.

The case is an application from Miss Sanaa Anjum, CNIC:37406-1522589-8, CEO, M/s Continuum Research Center, First Floor, Anwaria Hotel Plaza, satellite Town and G.T. Road, Wah Cantt, wherein the request has been made for license to act as Clinical Research Organization (CRO). The application is on prescribed Form-I of the Bio-Study Rules 2017 along with a fee of Rs.300000/- submitted vide Slip number 40944702672, dated 18th October 2022.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed fee challan	Rs.300000/- submitted vide Slip number 40944702672, dated 18th October 2022.
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	Sole Proprietor, Rental agreement 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.	**Firm has attached list of laboratory equipment although not applicable 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. Sanaa Anjum	MSc Math, M.Phil, PhD	Statistical Data Manager
Dr. Arfaat Yameen	B Pharm. M. Phil, PhD	Director research Evaluation and Collaboration
Dr. Abid Saeed Baig	B Pharm. M. Phil, PhD	Director Regulatory Affairs and Coordination.
Dr. Muhammad Sami	B Pharm. M. Phil, PhD	Research project Head
Dr. Nargis Amaan	B Pharm. M. Phil, PhD	Senior Research Analyst
Miss. Laiba Hasrat	B Pharm. M. Phil,	Research Analyst
Mr. Miss Ayesha Awan	B Pharm. M. Phil,	Research Analyst
Mrs. Ahmad Usman	B Pharm. M.S.	Manager Research Coordination & Management
Mr. Furqan Mushtaq	B. Com	Manager Accounts and Finance
Mr. Abubakar Noman	M.Sc. Computer Science, MS	Data Analyst & Management / IT

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

i. Medical Function
ii. Regulatory Submission Team
iii. Clinical Operations
iv. Data Management
v. Biostatistics
vi. Medical Writing
vii. Quality Assurance
viii. IT Team

ix. Admin & Finance
x. Human Recourse
xi. Training & Development.

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

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

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

7. The shortcomings were communicated to the applicant vide this office letter dated F.No. 15-20/2022 DD (PS) dated 2nd February 2023.

8. The reply submitted by Dr. Sanaa Anjum, CEO, Continuum Research in response to this office letter F.No. 15-20/2022 DD (PS) dated 2nd February 2023, that has been written below in tabulated form:

S.No.	Queries/ Shortcomings	Reply
1	Submit the Division, along with details of staff working in these division, as per divisions approved by Clinical Studies Committee.	Applicant has given nine different divisions and has amended the organogram accordingly.
2	The employees working in different Divisions should be full time employee of Contract Research Organization.	Applicant has submitted appointment letters.
3	Government Employee should submit NOC for permission to work in other organization.	Applicant has stated that no government employee is on Board.
4	MOU with City Pharmacy, Brooklyn Pharmaceuticals and Ali Pharmacy are with Wah College of Health Sciences instead of Continuum Research Organization.	Applicant has submitted MOUs.
5	Laboratory Equipment list attached with application. Role of this equipment in Contract Research Organization may be defined.	The Lab equipment will be used for training of Human Resources.
6	Clinician/ physician should be the part of CRO Team.	Copy of the appointment letter attached.

9. Meanwhile the following panel constituted vide this office letter F. No. 15-20/2022 DD (PS) dated 22nd February 2023 inspected the premises on 21.03.2023.

i. Dr Faiza Bashir, Member CSC/ National Coordinator, NBC, Health Research Institute (HRI), G-5/2, Islamabad.
ii. Mr. Malik Muhammad Asad, Deputy Director, DRAP, Islamabad (**Coordinator**).
iii. Mr. Muhammad Nouman Yousaf, Deputy Director (PS), DRAP, Islamabad.

10. The panel has submitted the inspection report as per checklist with following remarks'

The panel appreciated the commitment of the management of CRO towards continual improvement. The human resources with relevant qualification, as well as equipment/ computers were installed, However, it was observed that training of staff on GCP & QMS were lacking. The SOPs and

documentation were not as per required standards, also the MOU presented ē Wah General Hospital was incomplete w.r.t Patients Safety required for clinical trials. (The hospital is not registered trial site). No IRB was available and the role of the CRO could not be explained clearly be the team Continuum. Furthermore, data handling, security and retrieval needs further improvement. Hence the panel unanimously decided to defer the grant of licence for further improvements.

- ***Deferred for Improvement.***

11. Secretary CSC presented the case before the Committee.

Decision:

The CSC in light of inspection report decided to defer the case for fulfillment of following shortcomings/observations recorded by the panel:

i. *Develop and document Standard Operating Procedures (SOPs) for all aspects of the CRO's operations, including document control, SOP creation, revision, and retirement, SOP review, CAPA, SOP deviations, change control, computer validation, clinical operations, vendor qualification, and record retention and archival.*
ii. *Ensure that personnel receive appropriate training and have documented personnel curricula and GCP/regulatory training records. Also, establish a system for personnel to report safety concerns or incidents.*
iii. *Find an appropriate facility that provides adequate security, confidentiality, cleanliness, and space for storing materials and equipment.*
iv. *MoU presented with WAH General Hospital is incomplete with respect to patient safety, required for Clinical Trials. Furthermore, the Hospital is not a DRAP licensed Clinical Trial Site*
v. *Develop and implement computer validation master plan and SOPs, including mechanisms for system validation, change control, error investigation, hardware maintenance, data backup, and preventative maintenance.*
vi. *Establish a dedicated facility/area for the archival of records and monitor the premises through cameras.*
vii. *Implement a system for electronic data archival.*
viii. *Ensure that all staff have job descriptions and training records.*
ix. *Establish a schedule for SOP review and update the current index listing of the SOPs.*
x. *Develop and implement SOPs for Clinical Operations that cover all aspects of study start-up, conduct, and closeout/completion.*
xi. *Establish an SOP for the retention, storage, and destruction of records.*

AGENDA ITEM X:

APPLICATION FOR APPROVAL OF LICENCE TO ACT AS CRO FROM M/S DIAKOB ENTERPRISES, ISLAMABAD. F. No.15-11/2022-CRO.

The case is an application from Dr. Maryam Khalid, CNIC: 6110l-63256624, CEO of M/S Diakob Enterprises, Flat # 413, 4th Floor, Golden Heights, F-11/1 Islamabad, Pakistan. Wherein they have requested for license of their firm with DRAP to act as Clinical Research Organization (CRO). The application evaluated according to pre-requisites as mentioned in Form-I of the Bio-Study Rules notified vide SRO 697(I)/2018, summary of submitted documents is as follows: -

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Clarification is required whether it is for CRO or Clinical trial sites
2	Prescribed fee challan	Not provided
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	The applicant has provided the ASIC (Australian Securities & Investment Commission) Certificate however 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

	its partners and in the case of company the name and address of the company and its directors).	partners and in the case of company the name and address of the company and its directors) in Pakistan is not provided .
4	Details of premises including layout plan of the site.	Single page layout plan is attached without any Justification of Divisions/sections for required purpose.

2. Following deficiencies are required to be submitted as required under Form-I of the Bio-Study Rules notified vide SRO 697(I)/2018.

i. Clarification is required whether it is for CRO or Clinical trial sites as both has been mentioned in the application.
ii. Prescribed processing fee is not submitted.
iii. The applicant has provided the ASIC (Australian Securities & Investment Commission) Certificate however 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) in Pakistan is not provided.
iv. Single page layout plan is attached without any Justification of Divisions/sections for required purpose.
v. Undertaking on affidavit is not submitted.

3. Reply submitted by the applicant in response to this office letter and is evaluated as under: -

S. No.	**Required Documents / Information**	**Remarks**	**Reply**
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Clarification is required whether it is for CRO or Clinical trial sites	Applicant has clarified that application is for CRO.
2	Prescribed fee challan	Not provided	Provided. Submitted vide challan 3067243906 dated 17-08-2022
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	The applicant has provided the ASIC (Australian Securities & Investment Commission) Certificate however 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) in Pakistan is not provided .	FBR document regarding legal status attached.

4. As per check list the applicant has submitted the deficiencies, if agreed the case may be placed before the CSC/Chairman CSC for constitution of panel of experts for further necessary action on the matter, please.

5. The following panel was constituted;

i. Director (Pharmacy Services), DRAP, Islamabad.
ii. Mst. Tehreem Sara, Area FID, DRAP, Islamabad.
iii. Ahsan-Ul-Haq Athar, DRAP, Islamabad.

6. Received the request from Mr. Khalid Mehmood, Director, Diakob Enterprises, Islamabad wherein he has requested that as Dr. Noor Muhammad Shah has been transferred recently to some other department, so the panel may be reconstituted.

The panel for inspection was constituted vide letter F.No. 15-11/2022 dated 2nd October 2022. The inspection could not be convened due to illness Mrs. Tehreem Sara and then transfer/ posting of the then Director (PS). The applicant was also contacted telephonically for inspection but was not responded.

7. The following panel was constituted:

i. Dr Faiza Bashir, Member CSC/ National Coordinator, NBC, Health Research Institute (HRI), G-5/2, Islamabad.
ii. Mr. Malik Muhammad Asad, Deputy Director, DRAP, Islamabad (**Coordinator**).
iii. Mr. Muhammad Nouman Yousaf, Deputy Director (PS), DRAP, Islamabad.

8. The panel was constituted vide this office letter F. NO. 15-11/2022DD(PS) dated 22 February 2023. The panel conducted the inspection on 21.03.2023. The panel has submitted the inspection report as per checklist with following remarks;

The inspection panel arrived at the premises on 21.03.2023 @ 1425 hrs., Mr. Khalid Mehmood (Director) was present at the time of inspection. It was observed that no signboard was affixed/ displayed outside the site, which was located at residential building. On enquiry, the panel was informed that if signboard is displayed it will be billed as commercial, since it is a residential building/ apartment. Furthermore, there was no HR/ Infrastructure and any facility for data handling, security & data analysis related to CRO, it was transpired that a residential building (apartment) is being utilized for commercial purpose. Hence the apartment/ proposed site is un-fit for conduct/ execution of research related activities, and unanimously recommended for rejection by the panel.

- ***Recommended for rejection.***

9. Secretary CSC presented the case before the Committee.

Decision:

The CSC after discussion/deliberations on inspection report decided to defer the case for fulfillment of following shortcomings/observations recorded by the panel:

Based on the observations made by the inspection panel, it is evident that the CRO "Diakob Enterprises" lacks basic organizational structure, standard operating procedures, appropriate facility, and data handling procedures. These deficiencies can lead to major issues in conducting clinical research, including compromised data quality, safety concerns, and regulatory non-compliance. Therefore, the following recommendations are made:

i. Establish a clear organizational chart with departments/divisions approved by CSC.
ii. Develop and document Standard Operating Procedures (SOPs) for all aspects of the CRO's operations, including document control, SOP creation, revision, and retirement, SOP review, CAPA, SOP deviations, change control, computer validation, clinical operations, vendor qualification, and record retention and archival.
iii. Ensure that personnel receive appropriate training and have documented personnel curricula and GCP/regulatory training records and job descriptions.
iv. Develop and implement computer validation master plan and SOPs, including mechanisms for system validation, change control, error investigation, hardware maintenance, data backup, preventative maintenance and SOP for the retention, storage, and destruction of records.
v. Establish a dedicated facility/area for the archival of records and monitor the premises.

vi. Implement a system for data archival.
vii. Install safety equipment such as fire extinguishers.

AGENDA ITEM XI:

APPLICATION FOR APPROVAL TO ACT AS CRO AT M/S HEALTHBEE PRIVATE LIMITED, LAHORE F. No.15-27/2023-CRO.

Application from Mr. Muhammad Ishaq Burney, Director, M/s Health Bee Projects Private Limited, E-02, 3rd Floor, Jasim arcade, Plaza No.64-65, Lane 1, Squares Commercial, Phase 7, Bahria Town, Islamabad, 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 302316228504, dated 27th December 2022.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached
2	Prescribed fee challan	Rs.300000/- submitted vide Slip number 302316228504, dated 27th 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).	SECP Certificate of Incorporation along with Memorandum of Association 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.	**N/A**
6	Names and qualifications of the above sections along with their staff.	The staff name and qualification of staff attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	**N/A**
8	Undertaking on affidavit	Attached

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

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

c. *Advised Pharmacy Services Division to prepare post trial variation list for review and consideration by CSC.*

4. In the light of above, it is proposed that panel may be constituted for the inspection of the premises for verification of the facility by the Chairman CSC.

5. Accordingly the following panel was constituted vide this office letter F. No. 15-27/2023-CRO dated 7th March 2023.

i. Mr. Malik Muhammad Asad, Deputy Director, DRAP, Islamabad.
ii. Mr. Muhammad Nouman Yousuf, Deputy Director (CT), DRAP, Islamabad (**Coordinator**).
iii. Mr. Abdul Mateen, Deputy Director (PV), DRAP, Islamabad.

6. The panel visited the premises 22.03.2023 and submitted the report as per checklist with following remarks:

The panel appreciated professional approach of CRO management and staff. HR and facilities with respect to data handling and integrity were found to be satisfactory. The IT department needs a few improvements which were highlighted by the panel. Management showed commitment to improve the facilities as advised. Based on the documents reviewed, people met and facility inspected, the panel has unanimously recommended for grant of licence as CRO.

- **Recommended for approval.**

7. Secretary CSC presented the case before the Committee.

Decision:

The CSC in pursuance to the recommendations of the inspection panel and in the light of discussion/deliberations decided to approve M/s Health Bee Projects Private Limited, E-02, 3rd Floor, Jasim arcade, Plaza No.64-65, Lane 1, Squares Commercial, Phase 7, Bahria Town, Islamabad, to act as Contract Research Organization under the Bio-Study Rules, 2017.

AGENDA ITEM XII:

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

The Case is the request from Dr. Ayaz Mir, Director, Shifa Clinical Research Center (SCRC), Islamabad, wherein he has enclosed application for renewal of licence for CTU (licence No. CTS-0026) situated at Shifa Clinical Research Center, Shifa International Hospital, Islamabad. The application is on Form-III of Bio-study Rules 2017 along with fee of Rs. 100,000/ deposited vise slip number 5886037321 dated 23.12.2022.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached.
2	Prescribed processing fee	Rs. 100,000/ deposited vise slip number 5886037321 dated 23.12.2022
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	Certificate of Incorporation issued by security exchange Commission of Pakistan is attached.
4	Details of premises including layout plan of the site.	Layout plan attached.

5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	List attached.
6	Names and qualifications of the management.	Attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Not attached.
8	Undertaking on stamp paper	Attached.

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

4. The case was placed before CSC in its 38th meeting held on 08 February 2023 and was decided as follow;
"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 F. No 15-14/2019-DD (PS) dated 22.02.2022.

a. Prof. Dr. Muzammil Hassan Najmi, Member Policy Board/ Prof. of Pharmacology, Foundation University, Islamabad.
b. Dr. Obaidullah, Director, Division of Pharmacy Services, DRAP, Islamabad.
c. Mr. Shafqat Hussain Danish, Assistant Director (PS), DRAP, Islamabad **(Coordinator).**

6. The following Panel visited the premises on 09.03.2023;

a. Prof. Dr. Muzammil Hassan Najmi, Member Policy Board/ Prof. of Pharmacology, Foundation University, Islamabad.
b. Dr. Obaidullah, Director, Division of Pharmacy Services, DRAP, Islamabad.
c. Malik Muhammad Asad, Deputy Director (PS), DRAP, Islamabad.
d. Mr. Shafqat Hussain Danish, Assistant Director (PS), DRAP, Islamabad **(Coordinator).**

7. The panel submitted the inspection report as per checklist on 07.04.2023 with following remarks: -

The panel appreciated commitment of CTS Team towards continuous improvements efforts of professionals in the team for growth and promotion of research culture in Pakistan was also acknowledge. Some areas requiring improvement were highlighted by the panel which are summarized as under: -

- *CTS does not have dedicated facility for trial related activities i.e. informed consent imp administration recovery post administration etc.*
- *Phase-I & II trials are applied but no dedicated intensive care facility is available owing to high bed occupancy rate of the hospital, trial subject safety is jeopardized.*
- *IMP is stored in central pharmacy without proper segregation, facility for storage and dispensing was also found to be unsatisfactory.*
- *Archiving facility was shifted to another building without intimation to DRAP. The facility was not inspected.*
- *There is a central pathological lab in the hospital, however, PK/PD testing is not available which will be arranged by the sponsor in-case of Phase-I and II clinical trials.*

Furthermore, it was observed that the walk-in OPD clinics and offices were being utilized for CT related activities and the trial related material (stationary and sampling kits) were inappropriately stored which is objectionable and contrary to GCP guidelines. Infectious waste and sharps were not also not properly disposed-off.

In the light of above mentioned observations, the panel has unanimously decided to defer the CTS for improvements.

8. Secretary CSC presented the case before the Committee.

Decision:

The CSC in pursuance to the recommendations of the inspection panel and in the light of discussion/deliberations decided to defer the case for fulfilment of following shortcomings as recorded by the panel:

i. *CTS does not have dedicated facility for trial related activities i.e. informed consent imp administration recovery post administration etc.*
ii. *Phase-I & II trials are applied but no dedicated intensive care facility is available owing to high bed occupancy rate of the hospital, trial subject safety is jeopardized.*
iii. *IMP is stored in central pharmacy without proper segregation, facility for storage and dispensing was also found to be unsatisfactory.*
iv. *Archiving facility was shifted to another building without intimation to DRAP. The facility was not inspected.*
v. *There is a central pathological lab in the hospital, however, PK/PD testing is not available which will be arranged by the sponsor in-case of Phase-I and II clinical trials.*
vi. *Walk-in OPD clinics and offices were being utilized for CT related activities and the trial related material (stationary and sampling kits) were inappropriately stored which is objectionable and contrary to GCP guidelines. Infectious waste and sharps were not also not properly disposed-off.*

AGENDA ITEM XIII:

NOTIFICATION OF EARLY TERMINATION OF CLINICAL TRIAL TITLED "A RANDOMIZED, BLINDED, PARALLEL CONTROLLED PHASE-III STUDY TO EVALUATE THE IMMUNOGENICITY AND SAFETY OF SARS-COV-2 MRNA VACCINE (LRVNA009) AS HETEROLOGOUS BOOSTER IN PARTICIPANTS AGED 18 YEARS AND OLDER VACCINATED 2 DOSES INACTIVATED SARS-COV-2 VACCINE" AT NIH AND AGA KHAN UNIVERSITY.F.No.03-07/2022-CT(PS).

The case is an application dated 27-03-2023 from Mrs. Ghazala Parveen, Chief, Biological production Division, NIH Islamabad wherein she has enclosed termination letter dated 15-02-2023 of the above Clinical Trial from the Sponsor:

Title	A Randomized, Blinded, Parallel Controlled Phase-III Study to Evaluate the Immunogenicity and Safety of SARS-COV-2 mRNA Vaccine (LRVNA009) as Heterologous Booster in Participants aged 18 Years and older Vaccinated 2 doses Inactivated SARS-COV-2 Vaccine
Protocol Number	LVRNA009-III-02
Investigational Vaccine	SARS-CoV-2 mRNA Vaccine (LVRNA009)
Sponsor of the Study	AIM Vaccine Co., Ltd AIM Innovation Biotechnology (Shanghai) Co., Ltd Ningbo Rongan Biological Pharmaceutical Co., Ltd LiveRNA Therapeutics Inc.
Reasons	**Timeline:** The approval of Clinical Trial conduction has taken more than 6 months **Covid-19 pandemic situation:** with continuous mutation of SARS-CoV-2 virus since the beginning of the pandemic, this CoVID-19 study vaccine (LVRNA009) that was designed to provide protection against the wild type strain may not be effective against emerging variant strains. **Loss of Strategic Interest:** The increased difficulties in obtaining approval of Covid-19 vaccine against wild type strain in China due to recent regulation updates.

2. As the decision of early termination of study comes before the study is initiated at both NIH and Aga Khan University, all clinical trial preparation activities should be discontinued.

3. Secretary CSC presented the case before the Committee.

Decision:

The CSC after discussion and deliberation acceded to the request of Mrs. Ghazala Parveen, Chief, Biological production Division, NIH Islamabad, regarding termination of Clinical Trial titled, "A Randomized, Blinded, Parallel Controlled Phase-III Study to Evaluate the Immunogenicity and Safety of SARS-COV-2 mRNA Vaccine (LRVNA009) as Heterologous Booster in Participants aged 18 Years and Older Vaccinated 2 Doses Inactivated SARS-COV-2 Vaccine", before initiation of the trial in Pakistan.

AGENDA ITEM XIV:

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

It is submitted that, subject trial was placed before CSC in its 39th Meeting held on 28th February, 2023. The Committee decided the case as follows:

Decision: -

The CSC after detailed discussion and deliberation decided;

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

- ***Phase-II***

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

- ***Phase-III***

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

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

2. A letter received from Prof. Dr. Muhammad Raza Shah, General Manager, CBSCR, International Center for Chemical & Biological Sciences, University of Karachi, dated 16th March, 2023. Wherein letter is in reference to this Division letter bearing even number F.No.16-39/2023-CSC, dated 03rd March, 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 03-14/2022-CT (PS)

This is with reference to the trial entitled "A Phase II/III. Multi-Center. Randomized. Blind. Positive-Controlled Study to evaluate the immunogenicity and safety of COVID-19 mRNA Vaccine (RBMRNA-405) as a booster dose in Adults who completed 2 doses of inactivated vaccination". The

subject trial was approved in 39th Clinical Study Committee meeting held on 28th February, 2023. Since the vaccine was designed for the protection against Omicron BA 1 and the Omicron BA 1 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 final application. The approval letter of the clinical trial is enclosed to this application.

4. It is submitted that, only decision of CSC was communicated, Registration Letter was not issued yet. In view of above, it is proposed that, the matter may be placed before CSC for consideration & decision, please.

Decision:

The CSC after discussion and deliberation acceded to the request of Prof. Dr. Raza Shah, Manager ICCBS- University of Karachi, Karachi, regarding close-out of Clinical Trial titled, "A Randomized, Blinded, Parallel Controlled Phase-III Study to Evaluate the Immunogenicity and Safety of SARS-COV-2 mRNA Vaccine (LRVNA009) as Heterologous Booster in Participants aged 18 Years and Older Vaccinated 2 Doses Inactivated SARS-COV-2 Vaccine", before initiation of the trial in Pakistan.

AGENDA ITEM XV:

APPLICATION FOR CONDUCT OF ALL CLINICAL TRIALS AT INDUS HOSPITAL & HEALTH NETWORK, KARACHI UNDER LICENCE NUMBER CTS-0047. F. No.15-05/2019-DD (PS)

Application is received from Dr. Naseem Salahuddin, Site Principal Investigator, end TB & endTB-Q Clinical Trials, Indus Hospital & Health Network, Karachi dated 24th March 2023. Wherein application is submitted for utilization generalized CTS licence number CTS-0047 for all Clinical Trials approved at Indus Hospital, Karachi.

2. Application is reproduced as under:

Subject: Application for Continuation of approved ongoing trial (End TB and End TB Q) in Indus hospital and Health Network (IHHN) under approved General License CTS-0047.
With reference to the DRAP inspection visit dated 2nd Mar2023, DRAP notified Indus Hospital of different Clinical trial licenses previously issued to Indus Hospital for continuation of clinical trial activity details of which are mentioned below:
l)No: CT-0005 Reference No: F.No.03-04/2019-DD (PS) dated 3rd February 2020 (end TB Evaluating Newly Approved Drugs for Multi drugs Resistant Tb) Phase -m Clinical Trial (end TB Clinical Trial).
2)CT-0006 F.No.03-17/2019-DD (PS) dated 3rd February 2020 (end TB Evaluating Newly Approved Drugs in Combination Regimens for Multi drugs Resistant Tb) with Fluoroquinolone Resistance (Q) (End TB-Q) Phase -m Clinical Trial.
Since Indus Hospital & Health Network is currently undergoing its trial operations under clinical trial site license CTS-0047 SERIAL NO: 0015, having validity till March 2024, while all other licenses have completed its valid period, it is requested that the endTB & end TB-Q trial also to be shifted to this license in order to complete its enrollment and trial subject follow up.
We look forward to your cooperation and positive response to comply all DRAP approved regulatory and study requirements.

3. Submitted for consideration & information, please.

Decision:

The CSC after discussion and deliberation decided to acceded the request for use of Generalized Clinical Trial Site licence number CTS-0047 of M/s Indus Hospital & Health Network, Karachi for all CSC approved Clinical Trial for The Indus Hospital & Health Network, Karachi, subject to provision of prescribed processing fee of Rs.25000/- under the Bio-Study Rules, 2017.

AGENDA ITEM XVI:

NOTIFICATION OF STUDY CLOSE-OUT REPORT FOR CLINICAL TRIAL TITLED, "CHLOROQUINE/ HYDROXYCHLOROQUINE PREVENTION OF CORONAVIRUS DISEASE (COVID-19) IN THE HEALTHCARE SETTING; A RANDOMISED, PLACEBO-CONTROLLED PROPHYLAXIS STUDY – COPCOV" AND REQUEST FOR DESTRUCTION OF UNUSED IMPS. F.NO. 03-43/2020-DD (PS)

It is submitted that, subject trial was approved by the CSC and registration letter number CT-0020 was issued on 28th August, 2020. Dr. Muhammad Asim Beg, Professor & Consultant Parasitologist, Aga Khan University Hospital, Karachi submitted a close-out report dated 05th October, 2022, along with an application for incineration/destruction of unused/expired IMPs. Applicant haven't provided prescribed processing fee.

- **Application-I**

Study Completion Report

Chloroquine/ Hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a randomised, placebo-controlled prophylaxis study (COPCOV).

DRAP Reference No: F.No.03-43/2020-DD(PS)

COPCOV

The study is a multi-country double-blind, randomised, placebo-controlled trial that was conducted in healthcare settings.

Rationale and Aim:

The crude mortality and high reproductive ratio indicate urgent need to determine effective preventive measures as the COVID 19 pandemic grows. The major threat to healthcare workers and other staff working in a facility where there are cases of either proven, or suspected COVID-19. To limit the spread using Chloroquine would be effective as it has significant antiviral activity against SARS-CoV-2 in cell culture, as it does for the related SARS-CoV. We hypothesize that chloroquine might both slow viral replications in exposed participants, attenuating or preventing the infection even if they are shown not to work in treatment or in post-exposure prophylaxis. It is a basic principle of infectious diseases that preventing an infection developing (i.e., preventing pathogen multiplication) requires less drug activity (i.e. lower doses or a less active drug) than treatment. In COVID-19 illness the total viral burden is orders of magnitude greater than at the time of initial infection. Indeed, viral burdens are often reducing by the time of hospitalization in COVID-19 so the window of opportunity for antiviral medicines is at the earliest stages of infection.

The primary objectives are to determine if prophylactic chloroquine or hydroxychloroquine prevents symptomatic COVID-19 illness. If proven effective this can be an affordable prophylactic treatment for health care workers.

Outcome measures:

Primary outcomes

The number of symptomatic COVID-19 infections will be compared between participants randomised to chloroquine or Hydroxychloroquine, and placebo groups.

Secondary outcomes

i. *The symptoms severity and duration of COVID-19 illness, in those who become infected during the study will be compared between the two groups using a respiratory severity score.*
ii. *The number of asymptomatic cases of COVID-19 will be determined by comparing serology in all participants at time of enrolment and at the end of follow up.*
iii. *The number and severity of symptomatic acute respiratory illnesses will be compared in participants randomised to chloroquine or Hydroxychloroquine, and placebo groups.*
iv. *Genetic loci and levels of biochemical components will be correlated with occurrence of and disease severity of COVID-19 or other Acute Respiratory Infections (ARIs).*
v. *The days lost to work, and the relationship between the subjective assessment of wellbeing and the decision to self-isolate when unwell (i.e. not go to work) will be examined in relation to the infection and treatment arm.*
vi. *The trial will collect data on use of health care resources and health related quality of life (EQ-5D-3L) to determine the effects between treatment groups.*

Pakistan Study Site (Aga Khan University Hospital) Summary:

Principle Investigator	*Total screened*	*Screen failures*	*Enrolled*	*Total SAEs*	*Total AEs*	*Total Pregnancies*	*Total Protocol Deviations*
Dr. M. Asim Beg	*1,293*	*644*	*649*	*02 (Already reported)*	*144 (Already reported)*	*04 (Already reported)*	*30 (Already reported)*

Study Close-out Monitoring:

Continuous remote monitoring was done by the sponsor and also at the end of the study. All queries were resolved.

Work to be done next year:

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

- **Application-II**

Subject: Unused Investigational Product to Incinerate

Dear Sir,

This is with respect to the trial ***"Chloroquine/ Hydroxychloroquine prevention of coronavirus disease (COVID-19) in the healthcare setting; a Randomised, placebo-controlled prophylaxis study (COPCOV)."***

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:

COPCOV (A004)

TOTAL IP RECEIVED	*TOTAL IP USED*	*TOTAL IP UN-USED*
40,000 Tablets (400 Boxes)	*28425 Tablets*	*11575 Tablets*

COPCOV (A012)

TOTAL IP RECEIVED	*TOTAL IP USED*	*TOTAL IP UN-USED*
40,000 Tablets (400 Boxes)	*20987 Tablets*	*19013*

2. Applicant may be asked to furnish all record regarding IMPs import and trial extension as the trial was approved for only 05 Months (w.e.f. 28th August 2020), whereas close-out report is furnished on 05th October 2022, along with prescribed processing fee of Rs. 25000/-

3. 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.

4. Secretary CSC presented the case before the Committee.

Decision:

The CSC decided that, the Chairman CSC constitute an expert panel for GCP-Compliance Inspection of the trial titled, "Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-19) in the Healthcare Setting; A Randomised, Placebo-Controlled Prophylaxis Study – COPCOV", 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:

COPCOV (A004)

TOTAL IP RECEIVED	TOTAL IP USED	TOTAL IP UN-USED
40,000 Tablets (400 Boxes)	28425 Tablets	11575 Tablets

COPCOV (A012)

TOTAL IP RECEIVED	TOTAL IP USED	TOTAL IP UN-USED
40,000 Tablets (400 Boxes)	20987 Tablets	19013

AGENDA ITEM XVII:

CLINICAL VALIDATION REPORT OF INVESTIGATIONAL ICU VENTILATOR "ALNNOVENT" MANUFACTURED BY THE ALSONS GROUP IN PAKISTAN. [03-68/2021-DD(PS).

The case is an "Clinical validation Report" of investigational ICU ventilator "Alnnovent" received in this office on 28-03-2023 from Principal Investigator, Dr. Hina Nabi Ahmed and other team members.

Trial venue:
Main ICU First Floor, Anesthesia / ICU Department, Allama Iqbal Medical College / Jinnah Hospital, Lahore.

Product Details:
Electro-mechanical ICU ventilator, AlnnoVent AVB-100.

- **Brief History of the Case:**

- **Discussion of the Subject Case in Clinical Studies Committee:**

The CSC in its 19th meeting held on 12-02-2021 constituted the following sub-committee to develop TORs and proforma for evaluation and inspection of application of investigational ICU ventilator "Alnnovent":

1. Biomedical Engineer
2. Anesthetist
3. Pulmonologist
4. Dr. Faiza Basheer
5. Prof. Dr. Javed Akram
6. Dr. Abdur Rasheed
7. Any other expert co-opted by the sub-committee.

2. The above-mentioned committee developed the TORs & submitted to the CSC for approval and the CSC in its 32nd meeting held on 12-10-2021 decided as follows: -

"To recommend the clinical validation application of ICU Medical Ventilator AlnnoVent AVB-100 developed by Alsons as per three newly approved TORs and proforma for evaluation and inspection of clinical validation of ventilator trial applications and furnish the results /reports in the sequence as approved by the Committee."

3. In the light of abovementioned TORs (Copy of TORs Annexed) the investigational ICU ventilator "Alnnovent" was inspected during the trial at ICU Department of Allama Iqbal Medical College / Jinnah Hospital, Lahore and submit the report (copy of report annexed) with following recommendations: -

- **The Recommendation of Ventilator by Investigators:**

"After 96 hour of validation trial, we found that AlnnoVent AVB-100 Ventilator may safely be used to ventilate patients in operation theaters and Intensive Care Unit for the purpose of continuous respiratory support under supervision of trained, qualified and authorized medical staff."

- **Suggestions by Investigators:**

Following are suggested to improve next upgrade of AlnnoVent AVB-100 ventilator:

i. To improve touch screen sensitivity
ii. To add humidifier
iii. To add built in compressor
iv. To upgrade into a user friendly and compact design
v. To add proper weaning modes of ventilation
vi. To increase the display/screen size
vii. Further extended time trial is advised to elaborate its functionality and continuous learning curve.

- **In the light of above, the case is submitted for consideration of CSC.**

Decision:

The CSC discussed the report at length in accordance to TORs and the following observations were recorded:

a. NBC approval issued on 03-09-2021, while trial report does not have the date of trial. The report received on 28-03-2023;
b. No patient categorization of the patients taken in the trial as per the TORs;
c. The NBC approval of the Ventilator was with the model no.EMD.Vent-03 while trial conducted have the model of AVB-100;
d. Number of total patients not mentioned;
e. Age of patients not mentioned;
f. No comorbidity noted/ mentioned in the report.
g. Patient clinical assessment not mentioned.
h. For how much time the Ventilator was attached to a patient, i.e., ≥ 06-hrs in TORs;
i. Ventilator parameters not mentioned in the report that shall be reported during the trial after 01-hour, 04-hour and 06-hour.

2. Accordingly, the Committee decided to constitute following sub-committee:

*i. Maj. General (Retd.) Aslam Khan, Professor of Pulmonology & Critical Care, Bahria International Hospital, Rawalpindi. (**Chairman**)*
ii. Head of Cardiology Department of Pakistan Institute of Medical Sciences, Islamabad or his Nominee.
iii. Prof. Dr. Iqbal Memon, Anesthetist/ Intensivist, Principal HBS Medical College Hospital, Tramri Chok, Islamabad.
iv. Director Pharmacy Services
v. Dr. Faiza Bashir, Nominee from the Member of CSC
vi. Biomedical Engineer from Medical Devices Board (MDB).
*vii. Dr. HM Jawad Ali, Deputy Director-PS (**Secretary**)*
viii. any co-opt member with approval of Chairman, sub-committee.

2. The sub-committee will review and evaluate the Clinical Validation Report of Investigational ICU Ventilator "ALNNOVENT" manufactured by the Alsons Group in Pakistan in the light of TORs developed for the Clinical validation of ventilators. The Sub-Committee will generate a comprehensive report to apprise the CSC. The sub-committee may invite PI during the evaluation process, if required.

AGENDA ITEM XVIII:

DELEGATION OF POWERS OF CLINICAL STUDIES COMMITTEE TO CHAIRMAN, CLINICAL STUDIES COMMITTEE.

Delegation of Powers of Clinical Studies Committee to Chairman, Clinical Studies Committee under Rules 13(9) of Bio-Study Rules-2017 in order to facilitate timely disposal of routine and day to day business of Clinical Studies Committee.

Sr. No.	Powers / Functions	Power delegated to
1.	Panel Constitution for inspection of CRO/BA&BE Center/Clinical Trial Site/Analytical Laboratory/Clinical Trial Study/BA&BE Study----prior to grant of license/approval and after approval for monitoring purpose.	Chairman, CSC
2.	Stoppage / Holding of Clinical Trial in case of emergency / untoward event of ADR.	Chairman, CSC
3.	Addition of already licensed Clinical Trial Site for registered Clinical Trial	Chairman, CSC
4.	Amendment in Protocol of Clinical Trial including change in number of subjects.	Chairman, CSC
5.	Amendment in Investigator Brochure.	
6.	Amendment in Informed Consent form	Chairman, CSC
7.	Extension of registration for a Clinical Trial after approval from NBC	Chairman, CSC
8.	Approval/Change of Technical Staff / Clinical Support Staff	Chairman, CSC
9.	Approval for import of quantity of IMP as per approved protocol.	Chairman, CSC
10.	Destruction of unused / expired IMP after Clinical Trial	Chairman, CSC
11.	Termination of Clinical trial before start of Study.	Chairman, CSC

2. Secretary CSC presented the case before the Committee.

Decision:

The CSC decided to defer the case for further deliberations. However, it was decided that, the powers delegated to Chairman CSC in the 38th meeting will continue to be exercised.

AGENDA ITEM XIX:

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

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

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

i. Name of Investigational product, including all available names & trade, generic or INN name etc.: **Peg-INF Injection Registration No.063211**

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

iii. **Purpose of trial:** The purpose of this study is to evaluate, easily accessible, cost-effective treatment for COVID-19 is required especially in a low resource setting such as Pakistan. Through our previous studies, we have shown that, individuals who show, limited signs and symptoms of COVID-

19 have a stronger immune response called the "Type-I Interferon response". Interferon can also be given as an injection and is commonly used to treat hepatitis viral infection. We propose to test the administration of PEG interferon in patients with COVID-19, a drug, and investigate its effect on the immune response and the ability of the body to clear the virus. To investigate the ability of peg IFN in symptomatic cases with minimal disease:

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

iv. Subject selection criteria:

a. Inclusion Criteria

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

b. Exclusion Criteria

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

c. Subjects recruitment & follow up processes:

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

Subject Follow up

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

Sampling Strategy:

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

Expected outcomes:

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

v. Number of subjects to be recruited: 24 Subjects

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

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs. 200,000/- deposited vide challan no. 983684863, dated 18th August, 2022.

3	Investigator Brochure (s)	As PEG-Interferon is a registered product, its PIL is attached in place of IB.
4	Final protocol	Attached but is not according to ICH-GCP Guidelines. Insurance details are not provided in protocol. **. Protocol is not signed by Sponsor & PI.
5	Informed consent and participant information sheet (Urdu to English)	Verbal/telephonic Consent Form are attached instead of Informed Consent Forms. It is informed that, ICFs as per ICH-GCP Guidelines need to be provided. * Compensation/Insurance details are not provided.
6	List of participating countries	Pakistan only.
7	Phase of trial.	Phase – II
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	24 Subjects 12 Active 12 Placebo. Details regarding placebo & its manufacturing & blinding of IMPs is not provided.
9	Site of the trial	Clinical Trial Unit, Aga Khan University Hospital, Karachi.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	AKUH IRB/ERC approval, dated 07th April, 2022 along with amendment approval letter dated 17th May, 2022 is attached. (Previously Dr. Faisal Mahmood was PI of the trial)
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter No.4-87/COVID-109/22/51, dated 21st July, 2022 (for a period of **Six** months).
12	CV's of the Investigators	CVs of PI, Zahra Hasan Ph.D. (Medical Microbiology) (65-67/Corr.)
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate of M/s BF Biosciences Ltd., 05-KM, Sundar, Raiwind Road, Lahore & CoPP for Peg-INF Injection (Peginterferon alpha-2a….180µg) mfd: by M/s BF Biosciences Ltd., Lahore is attached.
14	Pre-clinical/clinical safety studies	Not provided as IMP is a registered product. PIL is attached.
15	Summary of Protocol	Attached but not as per ICH-GCP Guidelines.
16	Summary of Investigator Brochure	As IMP is a registered product. PIL is attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Total 24 COVID-19 positive Subjects.
19	Name of Monitors & Clinical Research Associate	---
20	Evidence of registration in country of origin.	---
21	Copy of registration letter (if registered in Pakistan)	Attached.
22	Sample of label of the investigational product / drug.	Attached label is a commercial one & not as per ICH-GCP Guidelines.
22	Duration of trial	Approximately 12 Months.
23	Undertaking on Stamp paper	Not provided.

4. After initial scrutiny following shortcomings are recorded:

i. Attached protocol is not according to ICH-GCP Guidelines.
ii. Insurance details are not provided in protocol.
iii. Protocol is not signed by Sponsor & PI.

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

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

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

Decision:

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

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

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

7. Accordingly, shortcomings were shared to applicant. PI/Applicant shared reply through email:

i) Attached protocol is not according to ICH-GCP Guidelines
Ans. The protocol has been amended to meet ICH-GCP guidelines.

ii) Insurance details are not provided in protocol
Ans. The sponsor will provide insurance cover for the event related to investigational product. The institution will provide indemnity for any negligence or malpractices if happened during trial by AKU employees. AKU's research insurance (which covers legal liability of AKU arising from research/study) will provide indemnity for any negligence or malpractices if they occur during trial by any AKU employees.
For health insurance of research subject due to any adverse impact of research, we are in the process of obtaining health insurance from EFU Life Insurance Company.

iii) Protocol is not signed by Sponsor & PI.

Ans. The protocol revised as per ICH-GCP guidelines. All additional information is provided as Appendices listed below. It has been signed by the PI who has also signed the undertaking. The MOU for the proposal is also attached here and is signed by both sponsor and PI.

- *Appendix 5: Signed agreement (Ferozsons and AKU)*
- *Appendix 7: CV of Investigator*
- *Appendix 8: Undertaking of Investigator*

iv) Recruitment of subject with any medical check-up & telephonic consent without any is not as per ICH-GCP Guidelines. It is informed that, ICFs as per ICH-GCP Guidelines need to be provided.

Ans. We have modified the protocol for recruitment of study subjects as described in the revised application. Study subject would be patients recently diagnosed as having COVID-19 through a positive SARS-CoV-2 respiratory sample. They will be identified either through the routine testing conducted by the AKUH Clinical Laboratories, or by our collaborating physicians at the Department of Medicine. The PI is Head, Section of Infectious Diseases and routinely treats and manages COVID-19 patients. Once a patient is identified, they will be contacted by the study team and informed about the Clinical Trial. If they consent, they would be asked to come to the Clinical Trials Unit (Visit 1) for an evaluation and recruitment. Written informed consent will be taken from study subjects, as would be a blood sample and a nasal swab specimen.
After consent, randomization of the intervention will be done through the CTU for administration of either the peg-IFN (180mg sub cutaneous) or placebo (saline) by the study team.

v) Compensation /Insurance details are not provided in protocol & in the ICF.

Ans. Insurance details are provided above in 'ii'. Compensation: the study subject will be offered for the two on-site visits to Clinical Trials Unit, AKU on day 1 and day 14. This would be Rs 2000 at Visit 1 (recruitment) and Rs 4000 at day 14 (PKR 4,000). Benefits: the study will pay for free blood testing for the patient at day 1, 7 and 14. Together with free SARS-CoV-2 PCR testing at day 7 and 14. There will not be any additional cost(s) to the study participant that might result from participation in this study.

vi) Attached label is a commercial one & not as per ICH-GCP Guidelines.

Ans. The label provided earlier is drug commercial label. Below labeling will be done one IMP before dispensing. Hard copy of label is attached with application.

- *Appendix 4A: PEG-INF Label (Peg Interferon Alpha 2a), CTU, AKU*
- *Appendix 4B: PEG-INF Commercial label*
- *Appendix 4C: PEG-INF Commercial detail*
- *Appendix 4D: PEG-INF DRAP certificate of pharmaceutical product*
- *Appendix 4E: PEG-INF DRAP registration letter*
- *Appendix 4F: PEG-INF DRAP sale certificate*

vii) As per protocol, IMPs will be administered at home and in case of emergency what can be done at home as for a Phase I/II clinical trial tertiary care facilities should be available for treatment of patients.

Ans. As per suggestions received from DRAP, the protocol for administration of IMP has been revised and now stated as: "the Study team will administer the IMP at the CTU of the Aga Khan University Hospital. After this, patients will be monitored for 30 min for any possible adverse effects."

viii) AKUH Clinical Laboratory is not approved as a Bio-Analytical Laboratory from DRAP to act as Laboratory for Clinical Trials. Further, Clarification required for PK/PD Studies if required in the subject Clinical Trials.

Ans. As per suggestions received from DRAP, the protocol for administration of IMP has been revised and now stated as: "Study team trained in administering IM vaccines will only be vaccinating the study participants following vaccination SOPs. Vaccinations will be administered in the CTU of the Aga Khan University Hospital which will monitor the patients for 30 min post vaccination and allow patient privacy."

ix) Procedure for blinding of Active & Placebo is not provided

Ans. the statistician of the study will prepared the randomization list and develop opaque envelops for each participants. CTU pharmacist will keep the envelops in log and key and will prepare the IP/placebo as per randomization number following subject ID. The pharmacist will keep all drug dispensing and accountability in control access in CTU pharmacy. For any emergency un-blinding the PI/ delegated person will formally notify the CTU pharmacist for unblinding. (CTU emergency code breaking attached)

x) Details regarding placebo, its manufacturing & blinding of IMPs is not provided.

Ans. Saline will be used as placebo. It will be manufactured by BF Biosciences Limited (a subsidiary of Ferozsons Laboratories LTD) in the form of single use vials. The statistician of the study will prepare the randomization list and develop opaque envelops for each participant. CTU pharmacist will keep the envelops

in log and key and will prepare the IP/placebo as per randomization number following subject ID. The pharmacist will keep all drug dispensing and accountability in control access in CTU pharmacy. For any emergency un-blinding the PI/ delegated person will formally notify the CTU pharmacist for unblinding.
This information is now provided in the revised proposal.

- *Appendix 3A: Emergency Code Breaking/Unbinding Document, CTU, AKU*
- *Appendix 3B: Good Clinical Trial Practice Document, CTU, AKU*

xi) Attached label is a commercial one & not as per ICH-GCP Guidelines.

Ans. The label provide earlier is drug commercial label. Below labeling will be done on IMP before dispensing. Hard copy of label is attached with application.

xii) Trial sponsor details are not provided.

Ans. The sponsor details are as below: M/s BF Biosciences Limited, 5 KM Sundar Raiwind Road, Raiwind Lahore 54010, Pakistan These details are now added in the revised proposal.

- Appendix 5: Signed agreement (Ferozsons and AKU)

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

Ans. Thank you for this observation. The PI has now been changed to Dr. Syed Faisal Mahmood, Associate Professor, Department of Medicine who is a Clinician and experienced clinical researcher. An undertaking from him is also enclosed. His CV is attached as part of the protocol.

- *Appendix 7: CV of Investigator*
- *Appendix 8: Undertaking of Investigator*

10. Secretary CSC presented the case before the Committee.

Decision:

The CSC after detailed discussion and deliberation decided to approve Clinical Trial titled, "Role of Peglyated Interferon in SARS-CoV-2 Viral Clearance and Immunologic Outcomes in COVID-19 Patient Using Blood Transcription Profiling" to be conducted at Aga Khan University Hospital, under supervision of Dr. Syed Faisal Mahmood, Associate Professor, Department of Medicine, AKUH, Karachi.

2. Following IMPs quantity is also approved for the trial:

- *Peg Interferon Alpha 2a Injections (Active) 12.*
- *Peg Interferon Alpha 2a Injections (Placebo) 12.*

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