MINUTES OF THE 34TH CSC MEETING HELD ON 13TH JANUARY 2022.

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The 34th Meeting of the Clinical Study Committee (CSC) was held on 13th January 2022 through Zoom under the chairmanship of Dr. Masud Ur Rehman, Director Pharmacy Services Division / Chairman (CSC), at the Committee Room, Drug Regulatory Authority of Pakistan, 4th Floor, T.F. Complex, Islamabad.

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

Sr. No.	Name	Designation
01	Dr. Masud Ur Rehman	Chairman CSC / Director, Division of Pharmacy Services-DRAP.
02	Ahmad Din Ansari.	Secretary CSC/ Additional Director, Division of Pharmacy Services-DRAP.
03	Prof. Brig. (R), Muzammil Hassan Najmi.	Professor of Pharmacology, Foundation University, Islamabad.

3. The following members attended, the meeting online through; Zoom:

01	Prof. Dr. Javed Akram.	Professor of Medicine, Physician, Vice Chancellor, University of Health Sciences, Lahore.
02	Dr. Faiza Bashir.	Chairman, Pakistan Health Research Council or his nominee, Islamabad.
03	Dr. Farhana Badar.	Biostatistician & Epidemiologist, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.
04	Dr. Naseem Salahuddin.	Director Infectious Diseases Indus Hospital, Karachi Co-opted Member.
05	Dr. Aamir Jaffary	Sindh Institute of Urology & Transplantation (SIUT), Karachi Co-opted Member.
06	Prof. Dr. Rizwana Chaudhri	HOD Gynecologist Holy Family Hospital, Rawalpindi Co-opted Member.
07	Prof: Dr. Mushtaq Ahmed	Professor of Cardiology, Bacha Khan Medical College, Mardan, KPK Co-opted Member.

4. The meeting started with the recitation of holy verses by Mr. Ahmad Din Ansari, Secretary CSC. The newly appointed Director, Division of Pharmacy Services/ Chairman CSC, Dr. Masud Ur Rehman, welcomed all the worthy members/co-opted members of the Committee & appreciated their active online participation through Zoom, during the entire tenure especially of Covid-19 pandemic.

General Discussion:

Before presentation of the agenda of the meeting, following general discussion was made:

On query regarding tenure of the CSC by Prof. Javed Akram, the Secretary apprised the Committee that term of the existing CSC will expire on 14-01-2022 and case for re-notification of the CSC is under submission for approval of Federal Government.

Dr. Aamir Jaffary suggested that a schedule for CSC meeting may be framed so that the members can mark those days for the said meetings. He also desired that for panel inspection, the panel members may be informed at least one week prior to the date of inspection. Prof. Dr. Javed Akram suggested that the Chair with the consent of CSC members may fix first Wednesday of every month except the public holiday for the said CSC meeting. Dr. Naseem Salahuddin emphasised to share the invitation letter of meeting along with agenda of meeting at least 7 days before the meeting day so that the members may have sufficient time to review the cases and technical documents. Dr. Mushtaq Ahmad also supported these proposals for efficient and smooth functioning of the Committee. Dr. Masud Ur Rehman, the Chair assured the CSC that he will try his level best to adopt all these valuable suggestions practically in the next tenure of Committee. Dr. Javed Akram also emphasized that some sort of reimbursement may be made to the members of inspection panel as the applicants/firms are charged by DRAP for processing all sort of cases of clinical research as well as their miscellaneous applications. Dr. Masud Ur Rehman, Chairman CSC expressed his gesture to the Committee with the remarks that the Division of Pharmacy Services will take up this matter with DRAP management for some practical solution to this effect in future.

The Chair after the above discussion asked the Secretary CSC to present the agenda of the meeting.

AGENDA ITEM I:

CONFIRMATION OF THE MINUTES OF THE 33rd CLINICAL STUDIES COMMITTEE MEETING.

1. Confirmation of Minutes of 33rd CSC meeting held on 11th November 2021. Since, the occurrence of Covid-19 pandemic majority of the meeting are being conducted online through zoom.
2. The minutes of the 33rd CSC meeting were shared with all CSC members through email on 15th November 2021. None of the comments/queries received from the members. Accordingly, decision of the meeting communicated. Minutes are placed again for confirmation to satisfy legal provision.

3. Submitted for confirmation of CSC.

Decision:

All the Members of the CSC unanimously confirmed the Minutes of 33rd CSC meeting held on 11th November 2021.

AGENDA ITEM II:

REQUEST FOR APPROVAL OF M/S AGA KHAN MATERNAL & CHILD CARE CENTER (AKMCCC), HYDERABAD TO ACT AS A PHASE-IV CLINICAL TRIAL SITE TO CONDUCT CLINICAL STUDY TITLED "A MULTICOUNTRY, MULTI-CENTER, THREE-ARM, PARALLEL GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIAL OF TWO DOSES OF ANTENATAL CORTICOSTEROIDS FOR WOMEN WITH A HIGH PROBABILITY OF BIRTH IN THE LATE PRETERM PERIOD IN HOSPITAL IN LOW-RESOURCE COUNTRIES TO IMPROVE NEW-BORN OUTCOMES". F.No.15-52/2021 DD (PS)

Application from Dr. Sayed Mairajuddin Shah (CNIC-42201-3587009-7), Chief Operating Officer (COO) Secondary Hospitals, Aga Khan University Hospital Karachi, for approval of M/s Aga Khan Maternal & Child Care Center (AKMCCC), situated at PLOT #4/2, Main Jamshoro Rd, Hyderabad-Sindh, to act as Clinical Trial Site for Phase-IV Clinical Trial titled, "*A Multicounty, Multi-Center, Three-Arm, Parallel Group, Double-Blind, Placebo-Controlled, Randomized Trial of Two Doses of Antenatal Corticosteroids for Women with A High Probability of Birth in the Late Preterm Period In Hospital In Low-Resource Countries To Improve New-Born Outcomes*" received on 09th December 2021. Application is on prescribed Form-I along with a prescribed fee of Rs.100000/- paid vide challan number 64042981, dated 08th November 2021.

2. After initial scrutiny summary of the application & attached 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 processing fee	Rs.100000/- paid vide challan number 64042981, dated 08th November 2021.
3	Particulars regarding the legal status of the applicant i.e. in the case of proprietorship the names of proprietors and their addresses, in the case of a firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	Attached.
4	Details of premises including layout plan of the site.	Attached.
5	Details of the section-wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Attached.
6	Names and qualifications of the above sections along with their staff.	Attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling, etc.	Attached.
8	Undertaking on stamp paper	Attached.

3. In view of above, it is proposed that inspection panel may be constituted by CSC, for verification of facilities available at the site to carry out proposed Phase-IV Clinical Trial as per GCP guidelines.

4. Submitted for consideration of CSC:

Decision:

The CSC after detailed discussion and deliberation decided to delegate the power to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference. The CSC further decided that panel members shall be informed at least five (05) days before inspection of the proposed site.

AGENDA ITEM III:

REQUEST FOR APPROVAL OF M/S AGA KHAN HOSPITAL FOR WOMEN & CHILDREN, KHARADAR, KARACHI TO ACT AS A PHASE-IV CLINICAL TRIAL SITE TO CONDUCT CLINICAL STUDY TITLED "A MULTICOUNTRY, MULTI-CENTER, THREE-ARM, PARALLEL GROUP, DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMIZED TRIAL OF TWO DOSES OF ANTENATAL CORTICOSTEROIDS FOR WOMEN WITH A HIGH PROBABILITY OF BIRTH IN THE LATE PRETERM PERIOD IN HOSPITAL IN LOW-RESOURCE COUNTRIES TO IMPROVE NEW-BORN OUTCOMES". F. No.15-53/2021-DD (PS)

Application from Dr. Sayed Mairajuddin Shah (CNIC-42201-3587009-7), Chief Operating Officer (COO) Secondary Hospitals, Aga Khan University Hospital Karachi, for approval of M/s Aga Khan Hospital for Women & Children, Kharadar, situated at Atmaram Pritamdas Rd, Lyari, Karachi, Sindh, to act as Clinical Trial Site for Phase-IV Clinical Trial titled, "*A Multicounty, Multi-Center, Three-Arm, Parallel Group, Double-Blind, Placebo-Controlled, Randomized Trial of Two Doses of Antenatal Corticosteroids for Women with A High Probability of Birth in the Late Preterm Period In Hospital In Low-Resource Countries To Improve New-Born Outcomes*" received on 09th December 2021. Application is on prescribed Form-I along with a prescribed fee of Rs.100000/- paid vide challan number 10557869, dated 08th November 2021.

2. After initial scrutiny summary of the application & attached 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 processing fee	Rs.100000/- paid vide challan number 10557869, dated 08th November 2021.
3	Particulars regarding the legal status of the applicant i.e. in the case of proprietorship the names of proprietors and their addresses, in the case of a firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	Attached.

4	Details of premises including layout plan of the site.	Attached.
5	Details of the section-wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Attached.
6	Names and qualifications of the above sections along with their staff.	Attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling, etc.	Attached.
8	Undertaking on stamp paper	Attached.

3. In view of above, it is proposed that inspection panel may be constituted by CSC, for verification of facilities available at the site to carry out proposed Phase-IV Clinical Trial as per GCP guidelines.

4. Submitted for consideration of CSC:

Decision:

The CSC after detailed discussion and deliberation decided to delegate the power to the Chairman CSC as was practiced previously for constitution of the inspection panel in the case under reference. CSC further decided that panel members shall be informed at least five (05) days before inspection of the proposed site.

AGENDA ITEM IV:

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

Application from Dr. Shabina Ariff, (CNIC-42301-3976716-8), Associate Professor & Consultant Pediatrician & Neonatologist, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi, for approval & registration of subject Clinical Trial/Study, received on 13th December 2021. Application is on prescribed Form-I along with a prescribed fee of Rs.200000/- paid vide challan number 9886981532, dated 07th December 2021.

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

i. **Name of Investigational product, including all available names; trade, generic or INN name etc.:**
   a. Dexamethasone 4mg/ml (Active) (amber ampoules)
   b. Dexamethasone placebo (normal saline) 1ml (amber ampoules)
   c. Betamethasone 4mg/ml (Active) (clear ampoules)
   d. Betamethasone placebo (normal saline) 1 ml (clear ampoules).

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

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

The aim of this multicenter trial is to assess the benefits and possible harms of two regimens of antenatal corticosteroids, dexamethasone phosphate 6mg IM and betamethasone phosphate 2mg IM compared to placebo administered q 12 hourly (total 4 doses) to pregnant women in the late preterm period (gestation age of 34^{+0} to 36^{+5} weeks) when they are at possible risk of preterm birth.

iv. **Primary Objective of the study:**

To compare the effect of an ACS regimen of dexamethasone phosphate 6mg q12h for 4 doses or until birth, whichever is earlier (Dexa-4x6mg) to placebo on a composite outcome of stillbirth, neonatal death or use of respiratory support within 72 hours of life, when given to pregnant women with a high probability birth in the late preterm period (34^{+0} to 36^{+5} weeks gestation) in hospitals in low resource settings.

2. To compare the effect of an ACS regimen of betamethasone phosphate 2mg q12h for 4 doses or until birth, whichever is earlier (Beta-4x2mg) to placebo on a composite outcome of stillbirth, neonatal death or use of respiratory support within 72 hours of life, when given to pregnant women with a high probability birth in the late preterm period (34^{+0} to 36^{+5} weeks gestation) in hospitals in low resource settings.

3. To compare the effect of an ACS regimen of dexamethasone phosphate 4x6mg q12h to a regimen of betamethasone phosphate 4x2mg IM q12h, on a composite outcome of stillbirth, neonatal death or use of respiratory support within 72 hours of life, when given to pregnant women with a high probability birth in the late preterm period (34^{+0} to 36^{+5} weeks gestation) in hospitals in low resource settings.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Prescribed processing fee	Fee of Rs.200000/- paid vide challan number 9886981532, dated 07th December 2021
3	Investigator Brochure (s)	Attached.
4	Final protocol	Protocol Version 1.1 attached. *Details regarding financing & insurance as per ICH-GCP guidelines are not described/included in the protocol.
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Pakistan, Bangladesh, Kenya, Nigeria & India.
7	Phase of trial.	Phase-IV
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Assuming * 2000-2500 patients will be recruited at your site over the life of the trial. the import quantities for your site over the life of the trial will be: i. 5714 amps of active dexamethasone 4mg/ml (amber amps) ii. 11429 amps of dexamethasone placebo (normal saline) 1ml (amber)

		iii. 2857 amps of active betamethasone 4mg/ml (clear) iv. 5714 amps of betamethasone placebo (normal saline) 1 ml (clear). These ampules will come packed in trays - one tray per participant. Each tray will contain 12 ampules. The identity of the ampules in the tray not be possible to decipher on visual inspection.
9	Site of the trial	i. Clinical Trial Unit, Aga Khan University Hospital Main Campus, Stadium Road, Karachi. (CTS-0003) ii. Aga Khan Hospital for Women, Garden, Karachi (CTS-0062) iii. The Aga Khan Hospital for Women & Children, Kharadar, Karachi (Application for approval received) iv. The Aga Khan maternal & Child Care Center (AKMCCC), Hyderabad (Application for approval received)
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Copy of AKUH-IRB/ERC approval dated 11th March 2021 is attached. * Original copy of Ethical approval from IRB/ERC also need to be provided to Division of Pharmacy Services-DRAP.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref:No.4-87/NBC-616/21/, dated 21st May 2021.
12	CV's of the Investigators	CVs of following (P.I/Co-PI) are attached: i. Dr. Shabina Ariff (PI), Associate Professor & Consultant Pediatrician & Neonatologist, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi. ii. Dr. Sajid Soofi (Co-PI), Professor & Associate Director, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi. iii. Dr. Lumaan Sheikh (Co-PI), Professor & Associate Director, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi. * PI & Co-PIs are from AKUH, Karachi, nominated PIs/Co-PIs from proposed sites are not described or included in the study.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Copy of GMP Certificates of following are attached:

		i. M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany. ii. Labesfal- Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal. Certificate of analysis of following IMPs are attached: iii. Betamethasone 4mg/ml Ampoules manufactured by M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany. iv. Betamethasone (Placebo) 4mg/ml Ampoules manufactured by M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany. v. Dexamethasone 4mg/ml, 1ml Injection manufactured by Labesfal- Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal. vi. Sodium Chloride0.9%, 1ml Injection manufactured by Labesfal- Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal. CoPP of following IMPs are not provided: i. Betamethasone 4mg/ml Ampoules manufactured by M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany. ii. Dexamethasone 4mg/ml, 1ml Injection manufactured by Labesfal-Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal.
14	Pre-clinical/clinical safety studies	Multiple research artless are attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Altogether 2000 to 2500 (70-100 Subjects/Month) will be enrolled from all study sites.
19	Name of Monitors & Clinical Research Associate	i. Dr. Atif Habib MBBS, MPH, PHD Director Projects and Assistant Professor Centre of Excellence women and child health Aga Khan University Hospital. ii. Dr. Khalil Ahmed FCPS (Pediatrics) Assistant Professor Department of Pediatrics and Child Health Aga Khan University Hospital.

		ii. Dr. Shah Mohammed MBBS, MPH, Senior Manager Centre of Excellence in Women and Child Health Aga Khan University Hospital. v. Dr. Adnan Mirza MBBS, MRCPCH, FRCP Assistant Professor Department of Pediatrics and Child Health Aga Khan University Hospital. * Monitors are from proposed trial sites instead of Co-PIs
20	Evidence of registration in country of origin.	Not provided & claimed as "Not Applicable".
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	30 Months
23	Undertaking on Stamp paper	Attached.

4. After initial scrutiny following shortcomings observed:

i. Details regarding financing/source of funding of the trial & insurance of trial participants as required by ICH-GCP guidelines are not described/included in the protocol. Applicant need to revise/amend study protocol & incorporate required details.
ii. Evidence for registration/approval of IMPs in country of origin is not provided.
iii. CoPP of following IMPs are not provided:
    a. Betamethasone 4mg/ml Ampoules (Active & Placebo) manufactured by M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany.
    b. Dexamethasone 4mg/ml, 1ml Injection (Active & Placebo) manufactured by Labesfal- Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal.
iv. Original copy of Ethical approval from IRB/ERC also need to be provided to Division of Pharmacy Services-DRAP.
v. Nominated PI & Co-PIs are only from AKUH, Karachi, Co-PIs should also from other proposed sites.
vi. Nominated monitors & Clinical Research Associates should be Co-PIs of the study from proposed Clinical Trial Sites.

5. Shortcomings communicated to applicant vide letter bearing number F. No.03-84/2021-DD (PS) dated 16th December 2021 yet response is awaited.

6. Submitted for consideration of CSC:

7. Dr. Shabina Ariff, Associate Professor, Agha Khan University, Karachi, the Applicant/ P.I of the study joined the meeting through Zoom & presented the case before CSC. PI also answered the questions raised by the CSC members.

Decision:

The CSC after detailed discussion and deliberation, ***deferred*** *the case for submission of soft copies of the protocol & investigator's brochure so as to share the same with expert members for their review and fulfillment of following shortcomings already communicated to the applicant:*

i. *Details regarding financing/source of funding of the trial & insurance of trial participants as required by ICH-GCP guidelines are not described/included in the protocol. Applicant need to revise/amend study protocol & incorporate required details.*
ii. *Evidence for registration/approval of IMPs in country of origin is not provided.*
iii. *CoPP of following IMPs are not provided:*
    a. *Betamethasone 4mg/ml Ampoules (Active & Placebo) manufactured by M/s Wasserburger Arzneimittelwerk GmbH, Herderstaße 1,2 und Molkerei-Bauer-Straße 18, Germany.*
    b. *Dexamethasone 4mg/ml, 1ml Injection (Active & Placebo) manufactured by Labesfal-Laboratórios Almiro, S.A, Zona Industrial do Lagedo, Santiago de Besteiros, 3465-157, Portugal.*
iv. *Original copy of Ethical approval from IRB/ERC of each Clinical Trial Site, also need to be provided to Division of Pharmacy Services-DRAP.*
v. *Nominated PI & Co-PIs are only from AKUH, Karachi, Co-PIs should also from other proposed sites.*
vi. *Nominated monitors & Clinical Research Associates should be Co-PIs of the study from proposed Clinical Trial Sites.*

2. Further, the Committee also asked the applicant to submit the reference studies of this nature/type that have been conducted in developed countries etc. and publication of such studies if any.

AGENDA ITEM V:

APPLICATION FOR APPROVAL OF M/S DEFENSE SCIENCE & TECHNOLOGY ORGANIZATION (DESTO), BIOLOGICAL RESEARCH CENTER (BRC), KARACHI TO ACT AS BIOANALYTICAL LABORATORY. F. No.15-51/2021 DD (PS)

Application is from Dr. Saifullah Khan, (CNIC:42205-2782657-5), Deputy Director General, Defense Science & Technology Organization (DESTO), Biological Research Center (BRC), Karachi. Wherein the request has been made to license the subject site with DRAP to act as Bioanalytical Laboratory, the application is on prescribed Form-I of the Bio-Study Rules along with a prescribed fee of Rs.300000/- submitted vide challan No. 5526958410, dated 04th November, 2021.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules.	Attached
2	Prescribed Fee	Fee of Rs.300000/- submitted vide challan No. 5526958410, dated 04th November, 2021 * It is submitted that the fee challan is not verified due to some system error, the matter is informed to MIS Division.
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 organization is a part of NECOM, SPD.

4	Details of premises including layout plan of the site.	Only layout attached.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Attached.
6	Names and qualifications of the above sections along with their staff.	Attached. * CVs of the staff also attached
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Attached. * Not applicable as the site is applied for Bioanalytical Laboratory.
8	Undertaking on stamp paper.	Attached.

3. In view of above, it is proposed that inspection panel may be constituted by CSC, for verification of facilities available at the proposed Bio-analytical laboratory as per requirements under the Bio-Study Rules 2017 & GCP guidelines.

4. Submitted for consideration of CSC:

Decision:

The CSC after detailed discussion and deliberation decided to delegate the power to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference. CSC further decided that, panel members shall be informed at least five (05) days before inspection of the proposed site.

AGENDA ITEM VI:

REQUEST FOR APPROVAL TO PROCURE STUDY VACCINE FOR CLINICAL TRIAL TITLED "IMMUNOLOGY & SAFETY OF HETEROLOGOUS COMBINATIONS OF COVID-19 VACCINES AVAILABLE UNDER EMERGENCY USE AUTHORIZATION IN PAKISTAN: ARANDOMIZED PHASE-II TRIAL" (COMBAT-COVID). F. No.03-85/2021-DD (PS)

Application is from Dr. Farah Naz Qamar, (CNIC-42201-8579891-2), Associate Professor, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi, for approval & registration of subject Clinical Trial/Study, received on 14th December 2021. Application is on prescribed Form-II along with a prescribed fee of Rs.200000/- paid vide challan number 070962990744, dated 07th December 2021.

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.:

S.No.	Investigational Product	Trade Name	Generic Name	INN Name
01	Sinopharm	Sinopharm	Inactivated SARS-COV-2	
02	CanSinoBIO	Convidecia™	Ad5-nCoV	

03	AstraZeneca	Covishield and Vaxzevria	Viral Vector Vaccine	COVID-19 Vaccine (ChAdOx)

ii. Sponsor:

This study is funded by Coalition for Epidemic Preparedness Innovations (CEPI). In collaboration with University of Oxford, International Vaccine Institute (Korea), Ragon Institute (USA), Harvard School of Medicine, (USA), CEPI central laboratories (VisMederi, Italy) and National Institute of Health (Islamabad).

iii. Estimated Cost of Project: 11,707,911 USD

iv. Sources of fund:

This study is funded by Coalition for Epidemic Preparedness Innovations (CEPI) which is an innovative global partnership between public, private, philanthropic, and civil society organizations. It was launched in Davos in 2017 to develop vaccines to stop future epidemics. CEPI has a mission to accelerate the development of vaccines against emerging infectious diseases and enable equitable access to these vaccines for people during outbreaks.

v. Study design & arms:

The study will enroll participants after obtaining informed consent and after enrollment the participants will be randomized in 9 study arms:

Group / Arm	First Dose	Second Dose	Booster Dose	SS*
1	BIBP (CNBG, SinoPharm) WIV	CanSino BIO		1680 (160 in each heterologous group and 240 in each homologous group)
2	BIBP (CNBG, SinoPharm) WIV	AstraZeneca ChAdOx		
3	CanSino BIO	BIBP (CNBG, SinoPharm) WIV		
4	CanSino BIO	AstraZeneca ChAdOx		
5	AstraZeneca ChAdOx	BIBP (CNBG, SinoPharm) WIV		
6	AstraZeneca ChAdOx	CanSino BIO		
7(ref)**	BIBP (CNBG, SinoPharm) WIV	BIBP (CNBG, SinoPharm) WIV	Six-month post second dose	
8(ref)**	CanSino BIO	CanSino BIO		
9(ref)**	AstraZeneca ChAdOx	AstraZeneca ChAdOx		

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

The purpose of this study is to evaluate the safety and immunogenicity of combinations of vaccines approved for use in Pakistan. This exploration meets emergency needs and may assist in the formulation of public health policies.

vii. **Primary Objective of the study:**

a. To determine whether the serum anti-spike IgG concentration against SARS-COV-2 four weeks post boost in COVID seronegative participants immunized with HPB COVID-19 vaccines regimens is non-inferior to that observed following homologous immunization (second dose at Day 70).

viii. **Secondary Objectives**:

a. To assess the safety and reactogenicity of different combinations of heterologous and homologous COVID-19 vaccines.
b. To characterize the neutralizing antibody response (pseudo-virus neutralization assay) against SARS-CoV-2 (as per schedule of events) in COVID seronegative participants immunized with HPB and homologous COVID-19 vaccines regimens.

c. To assess trend in immunogenicity (anti-spike IgG, anti-nucleocapsid) against SARS-COV-2 as per schedule events in COVID seronegative participants immunized with HPB and homologous CVODI-19 vaccines regimens.
d. To assess safety and immunogenicity of homologous full dose versus fractional dose homologous booster as compared to no booster at 6 months following the second dose of primary series among the participants in homologous arms.

ix. Details of Investigators & Roles:

Role	**Name**	**Affiliated Organization**	**Responsibilities**
Principal Investigator (PI)	Farah Naz Qamar	Aga Khan University Hospital, Pakistan (AKU)	Project design, protocol development, site visits and project supervision, data monitoring and analysis, report writing. Dissemination of results (reports, manuscripts). Overall project coordination.
(Co-I)	M. Tahir Yousafzai	AKUH	Project design, protocol development, field supervision and monitoring, guided data analysis, site supervision, report, and manuscript writing.
(Co-I)	Zahra Hassan	AKUH	Project design, protocol development, standardizing lab protocols, guided data analysis, supervision of lab analysis, report, and manuscript writing.
(Co-I)	Junaid Iqbal	AKUH	Project design, protocol development, standardizing lab protocols, guided data analysis, supervision of lab analysis, report, and manuscript writing
(Co-I)	Kiran Iqbal	AKUH	Standardizing lab protocols, guided data analysis, supervision of lab analysis, report, and manuscript writing.
(Co-I)	Sonia Qureshi	AKUH	Project design, protocol development, field supervision and monitoring, guided data analysis, report, and manuscript writing.
(Co-I)	Maria Fletcher	AKUH	Project design, protocol development, standardizing lab protocols, guided data analysis, supervision of lab analysis, report, and manuscript writing.
(Co-I)	Najeeha Iqbal	AKUH	Standardizing lab protocols, guided data analysis, supervision of lab assays, report, and manuscript writing.
(Co-I)	Momin Kazi	AKUH	Field supervision and monitoring, and eCRFs designing.
(Co-I)	Shazia Sultana	AKUH	Field supervision and monitoring, site supervision, and CRFs development.
National and International Collaborators			
(Co-I)	i. Andrew Pollard ii. Matthew Snape iii. Teresa Lambe iv. Xinxue Liu	University of Oxford	Scientific, technical, and clinical support, Biostatistics and data management support, and clinical samples testing support.
(Co-I)	i. Anh Wartel ii. Jean-Louis Excler iii. Deok-Ryun Kim	International Vaccine Institute (IVI), Korea	Scientific, technical, and clinical support. Biostatistics and data management support.
(Co-I)	Galit Alter	Ragon Institute,	Support in system serology assays.

		Harvard School of Medicine, USA	
(Co-I)	i. Maj. Gen. Aamir Ikram. ii. Ghazala Parveen iii. Firdous Nawaz Khan iv. Omera Naseer	National Institute of Health (NIH) Pakistan	Central Vaccine storage and management. Technical, advisory, and laboratory support. Support in obtaining regulatory approvals.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Prescribed processing fee	Fee of Rs.200000/- paid vide challan number 070962990744, dated 07th December 2021.
3	Investigator Brochure (s)	i. COVID-19 Vaccine (Vero Cells) Inactivated manufactured by Beijing Institute of Biological Products. Version 3.1 dated 19th April 2021. ii. AZD1222 - A recombinant chimpanzee adenovirus expressing the severe respiratory syndrome- coronavirus-2 Spike (S) surface (SARS-CoV-2) glycoprotein. Version 3.1 dated 05th July 2021. iii. Recombinant Novel Coronavirus Vaccine (Adenovirus Type 5 Vector). Version 1.2 dated 07th April 2021.
4	Final protocol	Protocol Version 1.1 attached.
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Pakistan, UK, Korea & USA.
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.	4500 Doses There are three different Vaccines, applicant has not provided justifications & quantities of different IMPs doses
9	Site(s) of the trial	i. Clinical Trial Unit, Aga Khan University Hospital Main Campus, Stadium Road, Karachi. (CTS-0003) ii. National Institute of Health, Park Road, Chak Shehzad, Islamabad.(CTS-0042) iii. Central Park Teaching Hospital, Lahore) (CTS-0049) * Applicant has not provided evidence for approval/ copy of trial site(s) approval. Further as per DRAP record, it is pertinent to mention here that, NIH, Islamabad is a phase-III trial specific approved site, Central Park Teaching Hospital, Lahore is approved for Phase-III & Phase IV Clinical Trials only & AKUH, Karachi has no facilities for

		Pharmacokinetic & Pharmacodynamic Studies facilities required in a Phase-II Clinical Trial. ** Following are mentioned as field sites for sample collection & as a laboratory: i. Aga Khan Hospital for Women, Karimabad, Karachi. ii. Aga Khan Hospital for Women, Garden, Karachi. iii. Isolation Hospitals & Infection Treatment Centre (IHITC), Islamabad. iv. Chughtai Lab & affiliated clinics Lahore. v. NIH Lab Islamabad. It is submitted that, under the Bio-Study Rules 2017 except Chughtai Lab Lahore, other mentioned sample collection/field sites & Laboratories are not approved by DRAP for Phase-II Clinical Trials. Applicant need to provide complete details regarding sites & laboratories involved or will be part of the trial and provide evidence of approval from DRAP.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Copy of AKUH-IRB/ERC approval dated 28th October 2021 is attached. Whereas, IRB/ERC approval from other proposed sites along with IRB/ERC composition need to be provided.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref:No.4-87/COVID-98/21/838 dated 26th November 2021.
12	CV's of the Investigators	CVs of following (P.I/Co-PI) are attached: i. Dr. Farah Naz Qamar (PI), Associate Professor, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi. ii. Mohammad Tahir Yousafzai iii. Prof. Zahra Hassan iv. Junaid Iqbal v. Kiran Iqbal Masood vi. Dr. Sonia Qureshi vii. Noshi Maria Fletcher viii. Iqbal, Najia Talat ix. Abdul Momin Kazi x. Andrew John Pollard xi. N.T. Anh Wartel xii. Jean Louis Excler, MD xiii. Deok Ryun Kim xiv. Mathew Snape xv. Teresa Lambe xvi. Xinxue Liu
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Not provided.
14	Pre-clinical/clinical safety studies	Attached, further preclinical studies data also attached in relevant IB of the IMPs.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Provided in IB of each IMPs.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	160 participants per heterologous group 240 per homologous group

		Total Subjects=1680
19	Name of Monitors & Clinical Research Associate	It is informed that, Sponsor/Applicant still looking for Monitors & Clinical Research Associate for the trial
20	Evidence of registration in country of origin.	Not provided.
21	Copy of registration letter (if registered in Pakistan)	Not provided.
22	Sample of label of the investigational product / drug.	It is claimed that, labels are attached as annexure-XIII, but actually not provided/attached in the file.
22	Duration of trial	30 Months (2.5 Year)
23	Undertaking on Stamp paper	Attached.

04. After initial scrutiny following shortcomings observed:

i. Evidence of approval/ copy of trial site(s) license(s) of proposed sites need to be provided.
ii. It is informed that, as per DRAP record, M/s NIH, Islamabad is a phase-III trial specific approved site, Central Park Teaching Hospital, Lahore is approved for Phase-III & Phase IV Clinical Trials only & AKUH, Karachi has no facilities for Pharmacokinetic & Pharmacodynamic Studies facilities as required in a Phase-II Clinical Trial, applicant need to submit clarification.
iii. Following are mentioned as field sites for sample collection & as a laboratory but as per DRAP record not approved for a phase-II clinical trial. Further, affiliated clinics of Chughtai Lab are not approved:
    a. Aga Khan Hospital for Women, Karimabad, Karachi.
    b. Aga Khan Hospital for Women, Garden, Karachi.
    c. Isolation Hospitals & Infection Treatment Centre (IHITC), Islamabad.
    d. Chughtai Lab affiliated clinics Lahore.
iv. It is submitted that, under the Bio-Study Rules 2017 except Chughtai Lab Lahore, other mentioned sample collection laboratories are not approved by DRAP for Phase-II Clinical Trials. Applicant need to provide complete details regarding sites, field sites & laboratories involved or will be part of the trial and provide evidence of approval from DRAP.
v. There are three different Vaccines to be used as IMPs, applicant need to provide justifications & quantities of each vaccine need to be imported or procured.
vi. Evidence of registration/ EUA of IMPs in country of origin is not provided.
vii. CoPP/EUA of Investigational Medicinal Products (IMPs) are not provided.
viii. GMP Certificate(s) of manufacturer of each IMPs are not provided.
ix. Ethical approval from each trial site's IRB/ERC along with complete composition of committee need to be provided.
x. It is claimed in the protocol that, volunteers for the trial will be identified by social mobilization, advertisement & communication. Whereas, material used for advertisement for trial recruitment is not provided with the application.
xi. It is claimed that, labels are attached as annexure-XIII, but actually labels of IMPs are not provided/attached in the file.

5. Shortcomings communicated to applicant vide letter bearing number F. No.03-85/2021-DD (PS) dated 17th December 2021.

6. Applicant/PI, Dr. Farah Naz Qamar, (CNIC-42201-8579891-2), Associate Professor, Department of Pediatrics & Child Health, Aga Khan University Hospital Karachi, for approval & registration of subject Clinical Trial/Study, submitted reply, received on 11th January 2022.

7. It is informed by the applicant that; the study site of Lahore is changed from Chughtai laboratories and clinics to Central Park Teaching Hospital for the study tilted "Immunogenicity and safety of heterologous combinations of COVID-19 vaccines available under Emergency Use Authorization in Pakistan: A randomized phase II trial."

8. Reply regarding shortcoming is as follows:

Shortcomings	Reply	Remarks
1. Only copy of licence of M/s AKUH, Karachi is provided. Evidence of approval/ copy of trial site(s) license(s) of proposed site(s) need to be provided.	We will not be performing any tests at these sites" These sites will be used for participant recruitment For recruitment and vaccination participants will come to the DRAP approved site of AKU which is the Clinical Trial Unit of AKU for enrollment. NIH DRAP phase-II trial license is attached. Central Park Teaching Hospital, Lahore is applying for phase-II trial approval in DRAP.	Any site involved in the trial for any of trial operation should be approved for that trial or trial phase by DRAP.
2. As per DRAP record, M/s NIH, Islamabad is a phase-III trial specific approved site, M/s Central Park Teaching Hospital, Lahore is approved for Phase-III & Phase IV Clinical Trials only & M/s AKUH, Karachi has no facilities for Pharmacokinetic & Pharmacodynamic Studies facilities as required in a Phase-II Clinical Trial, applicant need to submit clarification.	The trial being conducted is a Phase-II vaccine trial, There is no requirement for pharmacokinetic or pharmacodynamic studies to be done for this vaccine trial. Hence, we will not be conducting any pharmacokinetic or pharmacodynamic tests.	Even pharmacokinetic or pharmacodynamic studies are not required in the trial, following proposed trial sites are not approved for Phase-II Clinical Trial by the DRAP: i. M/s NIH, Islamabad. ii. M/s Central Park Teaching Hospital, Lahore. ii. Aga Khan Hospital for Women, Karimabad, Karachi. v. Aga Khan Hospital for Women, Garden, Karachi. v. Isolation Hospitals & Infection Treatment Centre (IHITC), Islamabad.
3. Following are mentioned as field sites for sample collection & as a laboratory but as per DRAP record not approved for a phase-II clinical trial. Further, affiliated clinics of Chughtai Lab are not approved: a. Aga Khan Hospital for Women, Karimabad, Karachi. b. Aga Khan Hospital for Women, Garden, Karachi. 4. Following are mentioned as field sites for sample collection & as a laboratory but as per DRAP record not approved as Clinical trial Site: a. Isolation Hospitals & Infection Treatment Centre (IHITC), Islamabad. b. Chughtai Lab affiliated clinics Lahore. 5. It is informed that, as per DRAP record except M/s Chughtai Lab Lahore, other mentioned sample collection laboratories are not approved by DRAP to act as laboratories for Clinical Trials under	There will be no lab tests performed at any of these sites. Only participant identification for recruitment will be done at these sites.	-do-

the Bio-Study Rues 2017. Kindly provide complete details regarding sites, field sites & laboratories involved or will be part of the trial and provide evidence of approval to act as Clinical Trial Site/Laboratory under the Bio-Study Rules 2017.		
6. There are three different Vaccines to be used as IMPs, applicant need to provide justifications & quantities of each vaccine need to be imported or procured.	The protocol was developed in the first quarter of 2021, at that time only these 3 vaccines were available in Pakistan for mass vaccination so only these were included in the study. Regarding quantities of vaccines, they have been calculated according to the sample size and the cohort distribution as mentioned on page no 28-29 of the protocol.	---
7. Evidence of registration/ EUA of Investigational Medicinal Products (IMPs) in country of origin is not provided. 8. CoPP/EUA of Investigational Medicinal Products (IMPs) are not provided. 9. GMP Certificate(s) of manufacturer of each IMPs are not provided.	The EUAs of these IMPs are already in DRAP Pakistan. This trial is funded by Coalition for Epidemic Preparedness Innovations (CEPI)and is based on commercially available vaccines, the manufacturers of vaccines are not part of this trial, so the GMP is not required as they are needed in only manufacture's-initiated trials.	Applicant need to provide EUAs of Vaccines utilized in the trial & GMP Certificates of manufacturer as required under Form-II of the Bio-Study Rules 2017.
10. Copy of AKUH IRB/ERC is provided. Whereas ethical approval from each trial site's IRB/ERC along with complete composition of committee need to be provided & IRB/ERC approval(s) should be in original.	AKU and NIH ERC approvals have been provided while application for approval has been submitted to IRBs of Lahore, IVI, and Oxford which will be shared soon once received.	IRB/ERC approval from all proposed / participating sites need to be provided.
11. It is mentioned in the protocol that, volunteers for the trial shall be identified by social mobilization, advertisement & communication. Whereas, material used for advertisement for trial recruitment is not provided with the application.		
12. It is claimed that, labels are attached as annexure-XIII, but actually labels of IMPs are not provided/attached in the file.	Labels are required for the IMPs which are in development phase however these are the commercially available vaccines and are also available in Government of Pakistan's vaccination program.	For labelling & masking of IMPs ICH-GCP guidelines need to be followed & sample label need to be provided. Further Vaccines (IMPs) should be labelled as "For trial purpose only"

9. After initial scrutiny of submitted reply following shortcomings has been observed;

i. As claimed even if pharmacokinetic or pharmacodynamics studies are not required in the trial, following proposed trial sites are not approved for Phase-II Clinical Trials by the DRAP:

a) M/s National Institute of Health, Islamabad.(The site is approved for specific Phase-III Trial) CTS-0042
b) M/s Central Park Teaching Hospital, Lahore. (The site is approved for Phase-III & IV Clinical Trials only) CTS-0049
c) Aga Khan Hospital for Women, Karimabad, Karachi. (The site is approved for Phase-IV Clinical Trials only) CTS-0061
d) Aga Khan Hospital for Women, Garden, Karachi. (The site is approved for Phase-IV Clinical Trials only) CTS-0062
e) Isolation Hospitals & Infection Treatment Centre (IHITC), Islamabad. (Application for the site not received yet)

ii. Any site involved in the trial for any of trial operation should be approved for that trial or trial phase by DRAP.
iii. Ethical approvals from IRB/ERC of all proposed / participating sites need to be provided.
iv. Evidence of registration/ EUA of Investigational Medicinal Products (IMPs) in country of origin is not provided.
v. CoPP/EUA of Investigational Medicinal Products (IMPs) are not provided.
vi. GMP Certificate(s) of manufacturer of each IMPs are not provided.
vii. For labelling & masking of IMPs ICH-GCP guidelines need to be followed & sample label need to be provided. Further Vaccines (IMPs) should be labelled as "For trial purpose only"

10. In view of above, it is proposed that, the applicant/PI advised to fulfill all prerequisites as per Form-II of the Bio-Study Rules 2017. Accordingly, DFA is prepared & attached. Further the case is placed before CSC for its consideration & decision, please.

11. Submitted for consideration of CSC:

12. Dr. Maria Fletcher and Dr. Muhammad Yousaf Zai of Agha Khan University, Karachi, joined the meeting through Zoom on behalf of PI & presented the case before CSC & also answered the questions raised by the CSC members. Dr. Ghazala Parween also joined the meeting through Zoom & requested that the license issued to NIH, Islamabad may be converted as a generalized trial site. She was responded by Secretary CSC that their applications(s) on the matter have been responded twice & that the CEO-DRAP was also briefed/apprised regarding the issue three to four days before & that they should apply afresh for approval of the site i.e. NIH, Islamabad as generalized trial site, if desired so.

Decision:

*The CSC after detailed discussion and deliberation, **deferred** the case for submission of soft copies of the protocol & investigator's brochure so as to share the same with expert members of the Committee for their review and fulfillment of following shortcomings already communicated to the applicant:*

i. As claimed even if pharmacokinetic or pharmacodynamics studies are not required in the trial, following proposed trial sites are not approved for Phase-II Clinical Trials by the DRAP:
a) M/s National Institute of Health, Islamabad.(The site is approved for specific Phase-III Trial) CTS-0042
b) M/s Central Park Teaching Hospital, Lahore. (The site is approved for Phase-III & IV Clinical Trials only) CTS-0049
c) Aga Khan Hospital for Women, Karim Abad, Karachi. (The site is approved for Phase-IV Clinical Trials only) CTS-0061
d) Aga Khan Hospital for Women, Garden, Karachi. (The site is approved for Phase-IV Clinical Trials only) CTS-0062
e) Isolation Hospitals & Infection Treatment Centre (IHITC), Islamabad. (Application for the site not received yet)
ii. Any site involved in the trial for any of trial operation should be approved for that trial or trial phase by DRAP.
iii. Ethical approvals from IRB/ERC of all proposed / participating sites need to be provided.

iv. *Evidence of registration/ EUA of Investigational Medicinal Products (IMPs) in country of origin is not provided.*
v. *CoPP/EUA of Investigational Medicinal Products (IMPs) are not provided.*
vi. *GMP Certificate(s) of manufacturer of each IMPs are not provided.*
vii. *For labelling & masking of IMPs ICH-GCP guidelines need to be followed & sample label need to be provided. Further Vaccines (IMPs) should be labelled as "For trial purpose only".*

AGENDA ITEM VII:

REQEST FOR APPROVAL OF THE ELIKIDS STUDY TITLED, "OPEN LABEL, TWO COHORT (WITH & WITHOUT IMIGLUCERASE), MULTICENTER STUDY TO EVALUATE PHARMACOKINETICS, SAFETY & EFFICACY OF ELIGLUSTAT IN PEDIATRIC PATIENT WITH GAUCHER DISEASE TYPE 1 AND TYPE 3. F.NO.03-83/2021 DD (PS).

Application is from Dr. Saba Abbasi, CNIC 42201-0571036-8, for M/s Sanofi Aventis, Medical Lead, M/s Sanofi Aventis , Karachi, dated 01st October 2021, on prescribed Form-II along with a fee of Rs.200000/- deposited vide challan No. 05834487331, dated 31st August 2021. Wherein request has been made for registration & approval of subject clinical trial, which will be carried out at M/s National Hospital & Medical Center, Lahore.

02. The details regarding trial design & sponsor is as under:

a. Study Arms & design:

Arms	**Intervention/treatment**
Experimental: Cohort 1: Eliglustat monotherapy Eliglustat for at least two years. Cohort 1 patients that experience significant clinical decline will receive rescue treatment. Rescue Treatment Step 1: Switch from eliglustat to imiglucerase monotherapy. Rescue Treatment Step 2: Patients who after 6 months of rescue therapy with imiglucerase monotherapy do not show improvement in the parameter(s) that led to the switch from eliglustat to imiglucerase, will then receive combination therapy with eliglustat + imiglucerase.	Drug: Eliglustat GZ385660 Pharmaceutical form: Capsule, Liquid Route of administration: Oral Other Name: Cerdelga
Experimental: Cohort 2: Eliglustat plus imiglucerase Eliglustat plus imiglucerase for two years, at the dose of enzyme replacement therapy received before enrollment. After Week 52, Cohort 2 patients will switch to eliglustat monotherapy for the remainder of the study if the desired clinical response has been achieved.	Drug: Eliglustat GZ385660 Pharmaceutical form: Capsule, Liquid Route of administration: Oral Other Name: Cerdelga Drug: Imiglucerase GZ437843 Pharmaceutical form: Powder for solution for infusion Route of administration: Intravenous Other Name: Cerezyme

i. **Sponsor:** M/s Sanofi Genzyme Corporation, 50 Binney Street, Cambridge, MA 02142, USA.

ii. Primary Objective of the study:

a. Assessment of pharmacokinetic (PK) parameter of eliglustat: Cmax [Time Frame: Weeks 2, 13, 26 and 52]
Maximum concentration (Cmax) of eliglustat in plasma

b. Assessment of PK parameter of eliglustat: AUC [Time Frame: Weeks 2 and 52]
Area under the plasma eliglustat concentration-time curve (AUC)

c. Adverse Events [Time Frame: Up to Week 364]
Number of adverse events in pediatric patients

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Prescribed processing fee	Rs.200000/- deposited vide challan no.05834487331, dated 31st August 2021
3	Investigator Brochure (s)	Attached. Number:GENZ-112638(GZ385660)-eliglustat Edition Number-16 Brochure for Cerezyme (imiglucerase) is not as per ICH-GCP guidelines.
4	Final protocol	Version 3.0 Protocol no. VV-CLIN-0225720 (Cerdelga®/ eliglustat/ GZ385660)
5	Informed consent and participant information sheet (Urdu to English)	Core Study Information & Informed Consent Form is attached. Whereas, compensation & insurance statement should be mentioned in the all ICF & all assent Form for children & adolescents which will be signed by Subject, Witness & Sponsor. Further, in the assent Form for children parents/ subject's legally acceptable representative signature should be added.
6	List of participating countries	Canada, Turkey, Argentina, Russia, Japan, United Kingdom, France, Italy, Spain, Sweden & 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.	• **Imiglucerase:** 228 vials per year & per patient, during 2 years. A minimum of 1824 vials of imiglucerase would be used in the trial, but considering a rate of 15% for kits damage, we anticipate a total number of approximately **2100** vials to be used in the trial • **Eliglustat:** 16 bottles of 60 capsules per year & per patient, during 4 years. So, a minimum of 256 bottles of eliglustat would be used in the trial but considering a rate of 15% for kits damage, we anticipate a total number of approximately **300** bottles to be used in the trial. * There are three different strengths (84mg, 42mg & 21mg) of Eliglustat Capsules, it is not described that which strength will be utilized in the trial & what quantities of each strength will be imported.

9	Site of the trial	Evidence (Licence issued by DRAP) of sites approval is not provided. Applied site (M/s National Hospital & Medical Center, Lahore) is approved as trial specific site. The site is not approved for Phase-III Clinical Trials.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref:No.4-87/NBC-659/21/237 dated 17th August 2021.
12	CV's of the Investigators	CVs of following (P.Is) are attached: iv. Dr. Huma Arshad Cheema, Professor / Consultant Pediatric Gastroenterology-Hepatology, Children Hospital & Institute of Child Health Lahore.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	• Un-signed GMP Certificate of following are attached: i. M/s Genzyme, Ireland Limited, Ireland. ii. M/s Sanofi-Aventis Recherche & Developpement, France. • Un-signed Manufacturer Authorization of following is attached; M/s Sanofi-Aventis Recherche & Developpement, France. • COA of following also attached; i. Eliglustat 21 mg Capsule (CAP B DRF 1 Clinical) ii. Eliglustat 50 mg Capsule (Pearlescent active clinical capsules) iii. Eliglustat 100 mg Capsule (Pearlescent active clinical capsules)
14	Pre-clinical/clinical safety studies	Eliglustat Clinical Trials & Registry publication links are provided. Whereas, data regarding Imiglucerase is not provided.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Summary for Eliglustat is attached. Whereas summary of Investigator's Brochure for Cerezyme (imiglucerase) is not provided.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Globally 60 Subjects For Pakistan: 04Subjects
19	Name of Monitors & Clinical Research Associate	Wajahat Imran. CV of CRA need to be submitted.

20	Evidence of registration in country of origin.	NDA Certificate No. 205494, issued by US-FDA is attached. European Commission is attached. No certificate is provided for Cerezyme (Imiglucerase) Solution for infusion from country of origin.
21	Copy of registration letter (if registered in Pakistan)	Copy of registration letter number 107918 in the name of M/s Sanofi-Aventis (Importer) for Cerezyme (Imiglucerase) Solution for infusion.
22	Sample of label of the investigational product / drug.	Sample of label of following IMPs are attached: i. Eliglustat 84 mg Capsule ii. Eliglustat 42 mg Capsule iii. Eliglustat 21 mg Capsule iv. Imiglucerase 400 IU (Powder for concentrate for solution for infusion)
22	Duration of trial	04 Years * The enrollment period will last on 30th March 2022 & the study duration for individual will be at least 2 years.
23	Undertaking on Stamp paper	Not provided.

4. Following additional trail related documents are also provided:

i. ELIKIDS Study Patient Diary, Version 1 (English & Urdu). (Page 537-548/Corr.)
ii. ELIKIDS Study Patient Diary, Unscheduled for Dose Adjustment, Version 1.(English & Urdu). (Page 549-560/Corr.)
iii. Dose Worksheet Version 1 (English & Urdu). (Page 561-565/Corr.)
iv. Visual Demonstration Card Version 1 (Page 566/Corr.)
v. Electronic Case Report Form (eCRF) (Page 568-570/Corr.)
vi. Matrix Blank CRF (Folders 7 Forms) (Page 571-1959/Corr.)

5. After initial scrutiny following shortcomings observed:

i. Provided Investigator's Brochure for Cerezyme (Imiglucerase) is not as per ICH-GCP guidelines & Summary of Investigator's Brochure for Cerezyme (imiglucerase) is not provided.
ii. Statement regarding compensation & insurance should be mentioned in all ICF & all assent forms for children & adolescents which will be signed by Subject, Subject's legally acceptable representative, Witness & PI/Sponsor.
iii. Further, Subject's legally acceptable representative signature should be added in the ICF/assent Form for children.
iv. There are three different strengths (84mg, 42mg & 21mg) of Eliglustat Capsules, it is not described that which strength will be utilized in the trial & what quantities of each strength will be imported.
v. Pre-clinical/clinical safety studies data regarding Cerezyme (Imiglucerase) is not provided.
vi. Applied site (M/s National Hospital & Medical Center, Lahore) was approved for Phase-IV Clinical Trial titled, "*Observational Study Program Assessing Effectiveness and Tolerability of Gliclazide 60 Mg Modified Release Tablet in patients with Type-II diabetes, fasting during Ramadan (Dia-Ramadan)*".
vii. Un-signed GMP Certificate of following are attached:
   a. M/s Genzyme, Ireland Limited, Ireland.
   b. M/s Sanofi-Aventis Recherche & Developpement, France.

viii. Un-signed Manufacturer Authorization of following is attached;
   a. M/s Sanofi-Aventis Recherche & Developpement, France.
ix. CoPP of following IMPs are not provided.
   a. Cerezyme (Imiglucerase) Capsule.
   b. Cerdelga (Eliglustat GZ385660), Powder for solution for infusion.
x. Details & CV of Clinical Research Associate need to be provided.
xi. It is mentioned in the application that, both IMPs will be imported but certificate is for Cerezyme (Imiglucerase) Solution for infusion from country of origin is not provided.
xii. Undertaking on Stamp paper is not provided.

6. Above mentioned shortcomings were communicated to applicant vide letter even number dated 28th October 2021.

7. Applicant Dr. Saba Abbasi, Medical Manager, M/s Sanofi Aventis, Karachi, submitted following reply on 10th November 2021.

S.No.	Shortcomings	Reply	Remarks
01	Provided Investigator's Brochure for Cerezyme (Imiglucerase) is not as per ICH-GCP guidelines & Summary of Investigator's Brochure for Cerezyme (imiglucerase) is not provided.	Cerezyme (Imiglucerase) is a commercialized product approved in Pakistan by DRAP. Therefore, we will use SmPC & IMPD. Both documents are enclosed again for convenience. (Page 1969-1996/Corr.)	---
02	Statement regarding compensation & insurance should be mentioned in all ICF & all assent forms for children & adolescents which will be signed by Subject, Subject's legally acceptable representative, Witness & PI/Sponsor.	Core Study Information and Informed Consent Form - Written subject information for patients that turn 18 years of age, version No. 4 dated 10-October-2019, on page 24 and 25 and Core Study Information and Informed Consent Form - Written subject Information for parents and Legally Accepted Representatives, Version No.4 dated 10-October-2019 on page no.25 and 26 it is described that they will be able to claim for study visit travel expenses and reasonable costs as meals, hotels. If due to the study treatment or procedures subjects are ill or need any treatment, the costs of that treatment will be covered by the study insurance and on "Core Pediatric Information and Assent Form statement for children (13 to 17 years), Version 4 dated 10- October'2019 the same statement as parents appears in section "compensation and expenses" from page 13.	---
03	Further, Subject's legally acceptable representative signature should be added in the ICF/assent Form for children.	There is a specific ICF for parents or LAR (legally accepted Representative) "Core Study Information and Informed Consent Form - Written subject Information for Parents and Legally Accepted Representatives, Version No.4 dated 1O-October-2019". There is also consent page (ln	---

		assent Form : Core Pediatric Information and Assent Form statement for children (13 to 17 years), Version 4 dated 10-October-2019;13-17 years old) on Page no. 12 and Written Subject Information (according to ICH/GCP 4.8 and Data Protection Requirements - Assent statement for children (6 to 12 years), Version 4 dated 10-October-2019 on Page No. 6 of each age there is another field so the LAR / Parents / witness must sign as well)	
04	There are three different strengths (84mg, 42mg & 21mg) of Eliglustat Capsules, it is not described that which strength will be utilized in the trial & what quantities of each strength will be imported.	In protocol amendment 3, section 8.2, it is described the different doses that will be administered depending on subject age, weight and metabolization profile. Hence the three strengths of eliglustat capsules will be imported as we can't anticipate the type of subject who will participate.	---
05	Pre-clinical/clinical safety studies data regarding Cerezyme (Imiglucerase) is not provided.	Imiglucerase (Cerezyme) is already approved by DRAP in Pakistan and approval letter is submitted. Preclinical and clinical studies data were previously submitted during product approval. Although imiglucerase is an investigational Medicinal Product in the ELIKIDS study, this will be used in combination with eliglustat as per protocol.	---
06	Applied site (M/s National Hospital & Medical Center, Lahore) was approved for Phase-IV Clinical Trial titled, "*Observational Study Program Assessing Effectiveness and Tolerability of Gliclazide 60 Mg Modified Release Tablet in patients with Type-II diabetes, fasting during Ramadan (Dia-Ramadan)*".	This site "National Hospital and Medical Center, Lahore is already approved for phase II-III-IV Clinical Trials and letter Dated 21 August 2019 is attached.	It was informed to applicant that, applied site is approved for a specific Clinical Trial, but applicant again submitted the same letter claiming that the site is approved.
07	Un-signed GMP Certificate of following are attached: M/s Genzyme, Ireland Limited, Ireland. M/s Sanofi-Aventis Recherche & Developpement, France.	Certified GMP Certificates are attached. (Page 2000-2010/Corr.)	---
08	Un-signed Manufacturer Authorization of following is attached; M/s Sanofi-Aventis Recherche & Developpement, France.	Certified Manufacturer's Authorization is attached. (Page 2011-2024/Corr.)	---

09	CoPP of following IMPs are not provided. Cerezyme (Imiglucerase) Capsule. Cerdelga (Eliglustat GZ385660), Powder for solution for infusion.	**a.** Eliglustat Certificates of Analysis from clinical batch were provided in the submission package. Find them enclosed again for your convenience. **b.** Find the Certificate of analysis of imiglucerase for bulk and vials. (Page 2029-2034/Corr.)	Applicant was asked to submit CoPP of following IMPs: a. Cerezyme (Imiglucerase) Capsule. b. Cerdelga (Eliglustat GZ385660), Powder for solution for infusion. But applicant provided again COA for the IMPs instead of CoPP Certificates.
10	Details & CV of Clinical Research Associate need to be provided.	CV of Clinical Research Associate is attached. (Page 2035-2037/Corr.)	---
11	It is mentioned in the application that, both IMPs will be imported but certificate is for Cerezyme (Imiglucerase) Solution for infusion from country of origin is not provided.	Marketed authorization granted by FDA for imiglucerase is provided. (Page 2039/Corr.).	It is submitted that, attached document is an NDA approval & its not a marketing authorization.
	Undertaking on Stamp paper is not provided.	Undertaking on Stamp Paper is attached (Page 2042/Corr.)	---

08. After review following shortcomings were recorded:

i. Applied site (M/s National Hospital & Medical Center, Lahore) was approved only for a Phase-IV Clinical Trial titled, "*Observational Study Program Assessing Effectiveness and Tolerability of Gliclazide 60 Mg Modified Release Tablet in patients with Type-II diabetes, fasting during Ramadan (Dia-Ramadan)*". See licence number CTS-0020, issued on 14th February 2020

ii. It was claimed that both IMPs used in the trial are approved & Marketing Authorization for Cerezyme (Imiglucerase) Solution for infusion issued by US FDA is attached, but attached document is NDA issued by US FDA.

iii. CoPP of following IMPs need to be submitted:
   a. Cerezyme (Imiglucerase) Capsule.
   b. Cerdelga (Eliglustat GZ385660), Powder for solution for infusion.

9. Above mentioned shortcomings were communicated to applicant vide letter even number dated 25th November 2021.

10. Applicant Dr. Saba Abbasi, Medical Manager, M/s Sanofi Aventis, Karachi, submitted following reply on 06th December 2021.

S.No.	Shortcomings	Reply	Remarks
01	Applied site (M/s National Hospital & Medical Center, Lahore) was approved only for a Phase-IV Clinical Trial titled, "*Observational Study Program Assessing Effectiveness and Tolerability of Gliclazide 60 Mg Modified Release Tablet in patients with*	The Letter Previously provided dated: 21 August 2012, "Approval of National Hospital & Medical Center", Lahore clearly mentioned that, "The CSC unanimously approved the National Hospital and Medical Centre, Lahore as Clinical Trial site for Phase II, III, IV for both outdoor and indoor Patients".	Applicant has not provided the copy of CTS licence issued for the proposed site. National Hospital & Medical Center, Lahore was approved for a Phase-IV clinical trial. During COVID-19 pandemic CSC

	Type-II diabetes, fasting during Ramadan (Dia-Ramadan)". See licence number CTS-0020, issued on 14th February 2020	The letter Dated 21st August 2019 is attached again. In addition to that, site is currently approved for Two - phase 3 trials, as mentioned below: The Site is currently approved for the two Phase 3 Trials: *1. A Phase III Randomized, Double Blind, Placebo Controlled Clinical Trial in 18 Years of Age and Above to Determine the Safety and Efficacy of ZF-2001, A Recombinant Novel Corona Vaccine (CHO Cell) For Prevention of COVID-19. F.No. 03-5212020 DD (PS)- Registration Number CT: 0023. Approved, Dated 19th March 2021.* *2. Phase III Study: A randomized double-blind controlled clinical trial ff DWJ1248 in prevention of COVID-19 infection after exposure of SARS COV-2 F. No.03-73/2021 DD (PS)*	approved the site for two clinical trials related to COVID-19 owing to situation of COVID-I9 pandemic in Pakistan in order to protect the patients. Applicant needs to provide copy of licence issued by the DRAP for the proposed trial site to support their claim regarding site approval or submit a new application for approval of proposed trial site.
02	It was claimed that both IMPs used in the trial are approved & Marketing Authorization for Cerezyme (Imiglucerase) Solution for infusion issued by US FDA is attached, but attached document is NDA issued by US FDA.	The NDA (New Drug Authorization) letters which were previously provided are the approved letter from FDA authorizing marketing / commercializing of the product, it is all published publicly on the FDA website. There are no other letter FDA issues. Please find attached the "FDA website screenshot for the reference, IMIGLUCERACE FDA approval Letter and original approval of IMIGLUCERASE support for Pediatrics use.	---
03	CoPP of following IMPs need to be submitted: a. Cerezyme (Imiglucerase) Powder for solution for infusion. b. Cerdelga (Eliglustat GZ385660) Capsule.	Cerezyme is a powder for solution for infusion (COA attached) and Eliglustat is a capsule (we provided all COA from the 3 strengths as part of the initial submission package). Attached again, 1. Certificate of Analysis - G2385660 EFC13738 OPEN LABEL SERIALIZED IMIGLUCERASE 2. Certificate of Analysis - IMIGLUCERASE (CEREZYME) 424 UNIT VIAL (400UN/10M1) POWDER FOR SOLUTION FOR INFUSION 4A1 3. Certificate of Analysis - Eliglustat 25 mg Cap. 4. Certificate of Analysis - Eliglustat 50 mg Cap.	Applicant submitting COA of the IMPs again & again. CoPP of following IMPs need to provided: a. Cerezyme (Imiglucerase) Powder for solution for infusion. b. Cerdelga (Eliglustat GZ385660) Capsule.

		5. Certificate of Analysis - Eliglustat 100 mg Cap.	

11. In view of above reply following shortcomings are recorded:

i. Applicant needs to provide copy of licence issued by the DRAP for the proposed trial site to support their claim regarding site approval or submit a new application for approval of proposed trial site.
ii. Applicant need to provide CoPP of following IMPs:
    a. Cerezyme (Imiglucerase) Powder for solution for infusion.
    b. Cerdelga (Eliglustat GZ385660) Capsule.

12. Shortcomings communicated to applicant vide letter bearing number F. No.03-85/2021-DD (PS) dated 28th October 2021& a reminder letter issued on 10th December 2021 & 11th January 2022, yet response is awaited.

13. Submitted for consideration of CSC:

Decision:

*The CSC after detailed discussion and deliberation, **deferred** the case for submission of soft copies of the protocol & investigator's brochure so as to share the same with expert members of the CSC for their review and fulfillment of following shortcomings already communicated to the applicant:*

i. Applicant needs to provide copy of license issued by the DRAP for the proposed trial site to support their claim regarding site approval or submit a new application for approval of proposed trial site.
ii. Applicant need to provide CoPP of following IMPs:
    c. Cerezyme (Imiglucerase) Powder for solution for infusion.
    d. Cerdelga (Eliglustat GZ385660) Capsule.

AGENDA ITEM-VIII:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED, "A MULTICENTER, RANDOMIZED, DOUBLE-BLINDED, PLACEBO-CONTROLLED STUDY TO ASSESS SAFETY AND EFFICACY OF SIR1-365 IN PATIENTS WITH SEVERE COVID-19)", PROTOCOL NO. SIR365-US-101. F. No.03-72/2021-DD (PS)

Drug Safety Utilization Report (DSUR) & application for destruction of expired/unused IMPs is from Dr. Syed Muhammad Sharib, Manager Medical Strategy & Clinical Operations, Metrics Research Pvt Ltd., Karachi (CRO for subject Clinical Trial), dated 14th July 2021.

2. Summary of the subject trial submitted is as follows:

EXECUTIVE SUMMARY

This is the first annual Development Safety Update Report (DSUR) submitted by Sironax USA, Inc. (Sironax) for the investigational drug SIRI-365. This DSUR was prepared in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) published guideline. ICH E2F Development Safety Update Report.

The development international birth date (DIBD) for SIR1-365 is 13 November 2019. This DSUR comprises safety data on all clinical studies ongoing and completed during the reporting period (13 November 2020 to 12 November 2021). The information provided herein is therefore based on available data as of 12 November 2021, the data lock point (DLP) for this DSUR.

SIR1-365 is a potent and selective allosteric kinase inhibitor of receptor-interacting protein 1 (RIP1). This inhibitor exhibits favorable properties both in vitro and in vivo. In animal Models, other RIP1 kinase inhibitors have demonstrated that blockade of RIP1 kinase activity prevents tumor necrosis factor alpha (TNFα)-induced systemic inflammatory response syndrome, the progression of Alzheimer's disease, amyotrophic lateral sclerosis, male reproductive system impairment, chemotherapy-associated kidney injury, ischemia reperfusion-induced organ injury including acute kidney injury (AKI). Colitis, and multiple sclerosis. With engineered kinase-dead RIP1, mice were resistant to chronic intestinal inflammation, autoimmune skin disorders, TNFα-induced systemic inflammatory response syndrome. and multiple sclerosis.

In cell-based and animal studies, SIR1-365 exhibits anti-inflammatory effects. Due to the unique chemical structure of this RIP1 inhibitor compared to other drugs in its class, SIR1-365 is in development as a new investigational drug tor the treatment of various degenerative and inflammatory diseases.

SIR1-365 has not been submitted for marketing authorization and is not authorized for use in any country or region.

At the time of this DSUR DLP, SIR1-365 has been administered as an oral formulation via tablet and oral solution at single doses from 10 to 600 mg and at 3 daily doses from 50 to 200 mg healthy adult volunteer subjects, 3 daily doses of 100 mg (300 mg/day) in subjects with severe COVID-19, and 2 daily doses of 200 mg (400 mg/day) in subjects with chronic prostatitis/chronic pelvic pain syndrome. Subjects have received SIR1-365 in 4 studies to date; exposure was determined from unblinded data for studies SIR365-AU-101 (healthy volunteers) and SIR365-AU-10-3 (healthy volunteers) and estimated based on blinded study data for studies SIR365-US-101 (subjects with severe COVID-19) and SIR365-AU-102 (subjects with chronic prostatitis/chronic pelvic pain syndrome). A total o1'164 clinical subjects have received SIRI-365 in these studies (142 healthy volunteers, 21subjects with severe COVID-19, and 1 subject with chronic prostatitis/chronic pelvic pain syndrome).

In studies of SIR1-365 in healthy volunteers, the most common treatment-emergent adverse events (TEAEs) were gastrointestinal disorders, headache, and somnolence. The majority of these TEAEs were mild and resolved. The following TEAEs were considered possibly or probably related to SIR1-365 in study SIR365-AU-101: abdominal discomfort, abdominal pain, alanine aminotransferase increased, dermatitis, diarrhea, dizziness, dyspepsia, flatulence, headache, myalgia, nausea, thrombocytopenia, tinnitus, tongue oedema, and ventricular extrasystoles. In study SIR365-AU-103, none of the TEAEs were considered related to SIR1-365, and they occurred at similar frequencies in the midazolam only cohort and the midazolam plus SIR1-365 cohort. Only I serious AE (SAE [humerus fracture]) occurred in healthy subjects who received SIR1-365 in these studies; however, this event was not considered related to study treatment. There were no serious adverse reactions (SARs) or deaths related to TEAEs in the healthy volunteer studies.

In study SIR365-US-101, 3 subjects experienced 5 TEAEs that were considered related to study treatment. These TEAEs were hypotension, orthostatic hypotension, paranesthesia oral, alanine aminotransferase increased and blood bilirubin increased. None of these TEAEs was considered serious. Additionally, 8 subjects in study SIR365-US-101 experienced 10 SAEs of pulmonary embolism (2), acute respiratory failure, hemoptysis, respiratory distress, respiratory failure, acute myocardial infarction, pneumonia, neck pain, and encephalopathy (1 each); however, none of these SAEs, which occurred in subjects who were hospitalized with severe COVID- 19, was considered related to study treatment. Further, no TEAEs were reported during the reporting period for 1 subject dosed in study SIR365-AU- 102.

No actions were taken for safety reasons during the reporting period; however, the Investigator's Brochure (IB) was updated 3 times during the reporting period to include data from the completed study SIR365-AU-101.

Overall, no specific safety signals, dose-dependent toxicity, or other trends were identified as risks for SIR1-365. Based on the clinical data to date, SIR1-365 may be considered to be safe and well-tolerated in single daily doses from 10 mg to 600 mg, multiple ascending daily doses from 150 mg to 600 mg, as a 100 mg oral suspension, in fed or fasted state, and when administered with omeprazole or midazolam.

The SIR1-365 safety profile, which is based on the first in-human studies in healthy adult volunteers and in subjects with severe COVID-19 or chronic prostatitis/chronic pelvic pain syndrome, suggests that the benefits of the effects of this drug outweigh any perceived risks, warranting further investigation in subject populations.

3. Further applicant Dr. Syed Muhammad Sharib, Manager Medical Strategy & Clinical Operations, Metrics Research Pvt Ltd., Karachi (CRO for subject Clinical Trial), submitted a request for destruction of Investigational Medicinal Products (IMPs) at two sites, dated 20th December 2021.

4. It is submitted that approved IMPs quantities for the subject trial were as follows:
   i. SIR1-365 (65 Bottles).

ii. Placebo (65 Bottles).
iii. Lab Kits=60 (Divided into two shipments)

5. Progress report of the trial is as follows:

Summary of work done during September to December 2021:

Number of planned participants around the globe: N:60 subjects and N=42 have been enrolled. Follows are the study updates in all sites of Pakistan.

Study Updates	**The Aga Khan University**	**Sindh Infectious Disease Hospital & Research**
Target recruitment (Planned)	20	20
Date of Start of Study (Screening Start)	30th August 2021	22nd September 2021
Total no. of subjects prescreened	114	69
Total no. of subject enrolled	03	09
Total no. of screen failures:	111	60
Date of End of Study (Last patient last visit)	30th October 2021	30th November 2021
Total no. of withdraw from the study	0l (without taking study drug)	02
Total number of subjects who have completed the study	02	07

6. Initially details regarding IMPs were not provided but after telephonic conversation, details forwarded through email. Details regarding IMPs utilization is as follows:

Study Updates	**The Aga Khan University**			**Sindh Infectious Disease Hospital & Research**		
Total no. of subject enrolled	03			09		
Total no. of withdraw from the study	01 (without taking study drug)			02 (01 Patient without taking study drug & 01 Patient with only one tablet consumption)		
Total number of subjects who have completed the study	02			07		
Investigational Products Received	66 Bottles (containing 1980 tablets, 30 tablets / each bottle), 2 Bottles for single Patient			64 Bottles (containing 1920 tablets, 30 tablets/ each bottle) 2 Bottles for single Patient		
Date of IP Receipt	17th August 2021			21st September 2021		
Investigational Products consumed	2 bottles were used			8 bottles were used		
	Bottle Number	*Tablet Consumed*	*Tablets Not-consumed*	*Bottle Number*	*Tablet Consumed*	*Tablets Not consumed*
	A0001	4	26	A0107	8	22
	A0003	4	26	A0108	7	23
				A0109	1	29
				A0111	8	22
				A0112	20	10
				A0113*	30	0
				A0114	13	17
				A0115	13	17
				A0116*	12	18
Investigational Products to be destructed	64 bottles (containing 1920 tablets) 02 Bottles (containing 52 tablets)			56 Bottles (containing 1680 tablets) 07 Bottles (containing 128 tablets)		

* One Patient remain enrolled for 14 days, consuming 42 tablets

7. In view of above it is proposed that, Development Safety Update Report (DSUR) is placed before CSC. Further a panel may be constituted by the CSC for verification of above-mentioned

IMPs quantities, supervision of destruction process & issuance of destruction certificate in accordance with ICH-GCP Guidelines & Conduct of Clinical Trial Guidelines.

8. Further applicant/PI may be directed to submit prescribed fee for miscellaneous request. Moreover, PI may be directed to keep expired/unused IMPs in safe custody.

9. Submitted for consideration of CSC:

Decision:

The CSC after detailed discussion and deliberation decided to delegate the power to the Chairman CSC, as was practiced previously; for constitution of the inspection panel in the case for the purpose of the destruction of the IMPs, available at the trial sites, as per SOPs provided by the Sponsor, the ICH-GCP Guidelines and the Conduct of Clinical Trials Guidelines issued by Division of Pharmacy Services DRAP. Further, the panel will also carry out audit of the conduct of the trial/study in the light of trial protocol & conditions of the trial registration/approval granted by the CSC.

AGENDA ITEM IX:

EXTENSION IN TRIAL DURATION OF CLINICAL TRIAL TITLED, "SCYNEXIS PROTOCOL NUMBER SCY-078-301, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SCY-078-305 (IBREXAFUNGERP) IN PATIENTS WITH FUNGAL DISEASES THAT ARE REFRACTORY TO OR INTOLERANT OF STANDARD ANTIFUNGAL TREATMENT (FURI)", FOR ONE YEAR F. No.03-61/2021-DD (PS)

Application for extension in trial duration is from Dr. Faisal Mahmood, Associate Professor and Sec: Head Medicine, Aga Khan University, Karachi, dated 07th September 2021. Wherein application following documents are attached:

i. Application for extension in trial duration along with progress report.
ii. Suspect Adverse Reaction Report.

2. Progress report of subject Clinical Trial is as follows:

Protocol Number: SCY-078-301
Sponsor: SCYNTEXIS, Inc
Principle Investigator: Dr. Faisal Mahmood
Centre: The Aga Khan University

1. Work done during the year: We received initial DRAP approval in March 2021. We did not recruit any subject in the study so far.
2. Problems encountered during the study: We were waiting for trial insurance from the sponsor as this is a phase III clinical trial. Recruitment process was slow due to stringent criteria.
3. Actions taken to solve the Problem: We received insurance on September 01,2021, and then assessed l8 potential patients but they did not meet the study criteria. Additional coinvestigators included in the study to expedite the process of recruitment.
4. Work to be done during next year: We will continue to recruit subjects based on inclusion criteria.

3. It is submitted that, the trial was approved on 31st March 2021 for 222 days & its registration will expire on 08th November 2021 & applicant submitted application for extension in the trial duration for another year.

4. Applicant provided following requisite documents:

i. Prescribed fee of Rs.25000/- submitted vide challan number 04952860463 dated 01st November 2021.
ii. IRB approval for extension in subject trial for one year, dated 09th September 2021.
iii. NBC approval for extension in subject trial for one year, Ref:No.4-87/NBC-584-Exten Y2/21/662, dated 26th October 2021.

5. Applicant also submitted quarterly progress report for Clinical trial titled, "Open-Labe Study to Evaluate the Efficacy and Safety of SCY-078 (Ibrexafungerp) in Patients with Fungal Diseases that are Refractory to or Intolerant of Standard Antifungal Treatment (FURI)" SCY-078-301" as follows:

Details of Principle Investigator

Name	Dr. Faisal Mahmood, Associate Professor & Sec: Head of Medicine
Address	Stadium Road, P.O Box 3500, Karachi
Email	Faisal.mahmood@aku.edu

Details of the Study

Protocol Number	SCY-078-301
DRAP Reference Number	F.No. 03-6112021-DD (PS)
Date of DRAP Approval	March 2021
Sample size of the study	15 subjects are expected to be enrolled
Sponsor of the study	SCYNEXIS,INC 1 Eventrust Plaza,13th Floor Jersey City, NJ 07302
Sample size of the study	15 subjects are expected to be enrolled
Number of Subjects Prescreened	We prescreened 67 subjects, out which 40 were Candidemia patients, 2 were Vulvovaginal Candidiasis and 25 were Aspergillosis patients
Number of Subjects Screened	Following 4 subjects were screened: 1. VVC, 2. Candidemia, 3. Chronic Pulmonary Aspergillosis (CPA), 4. Allergic Bronchopulmonary Aspergillosis (ABPA)
Number of Screen Failures	1 subject (CPA)was screen failed due to history of anticonvulsant medication
Number of withdrawals from study	1 subject (VVC) withdrawal voluntarily after consent
Number of Subjects Enrolled and Ongoing	2 subjects are enrolled (Candidemia and ABPA)
Severe Unexpected Serious Adverse Reaction (SUSAR)	Following SUSARs are reported from the other sites o the study: (Copy Attached) Acute hearing loss Muscle pain
Major Protocol Deviations	None
Serious Adverse Events	None

7. In view of above, progress report is placed before CSC for appraisal & request for extension in trial duration for another year as per NBC approval, please.

6. Submitted for consideration of CSC:

Decision:

The CSC after detailed discussion and deliberation decided to grant extension in the duration of the Clinical Trial titled, "Scynexis Protocol Number SCY-078- 301, Open-Label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of SCY-078-305 (Ibrexafungerp) In Patients with Fungal Diseases That Are Refractory to or Intolerant of Standard Antifungal Treatment (FURI)", for another year, as approved by the National Bioethics Committee.

AGENDA ITEM X:

EXTENSION IN TRIAL DURATION OF CLINICAL TRIAL TITLED, SCYNEXIS PROTOCOL NUMBER SCY-078-305, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SCY 078 (IBREXAFUNGERP) IN PATIENTS WITH CANDIDIASIS INCLUDING CANDIDEMIA, CAUSED BY CANDIDA AURIS. (CARES)", FOR ONE YEAR F. No.03-15/2019-DD (PS)

Application for extension in trial duration for another year is from Dr. Faisal Mahmood (PI) dated 02nd November 2021. It is submitted that, previously the application was placed before CSC in its 32nd CSC meeting held on 12th October 2021, the Committee decided the case as follows:

Decision:

The CSC after deliberation / detailed discussion decided to defer the case of extension in the Clinical Trial titled, "Open-Label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of SCY 078 (IBREXAFUNGERP) in Patients with Candidiasis Including Candidemia, Caused by Candida Auris", for fulfillment of all identified/already communicated prerequisites.

2. Shortcomings & CSC decision was shared with applicant after which applicant provided following requisite documents:

i. Application for extension in trial submitted with original signatures in original. (Page 1452-1453/Corr.)
ii. Prescribed fee of Rs.25000/- submitted vide challan number 377950102546, dated 05th October 2021. (Page 1451/Corr.)
iii. IRB approval for extension in duration for another year (w.e.f.10th June 2021) (Page 1451/Corr.)
iv. NBC approval Ref: No.4-87/NBC-421-Exten/21/651 issued for extension in duration for another year (w.e.f. 26th October 2021) (Page 1455/Corr.)

3. Further it is submitted that the applicant, Dr. Faisal Mahmood, Associate Professor and Sec: Head Medicine, Aga Khan University, Karachi, submitted a quarterly progress report dated 14th December 2021. Quarterly progress report is as under:

Details of Principle Investigator

Name	Dr. Faisal Mahmood, Associate Professor & Sec: Head of Medicine
Address	Stadium Road, P.O Box 3500, Karachi
Email	Faisal.mahmood@aku.edu

Details of the Study

Protocol Number	SCY-078-305
DRAP Reference Number	F.No. 03-15/2021-DD (PS)
Date of DRAP Approval	August 2020
Sample size of the study	15 subjects are expected to be enrolled

Study Recruitment Activities

Number of Subjects Prescreened from September to November 2021	08
Number of Subjects enrolled from September to November 2021	00
Difficulties in enrolment	Enrolment of the study has been halted for now. We are anticipating trial extension from DRAP
Severe Unexpected Serious Adverse Reaction (SUSAR)	Following SUSARs are reported from the other sites of the study: (Copy Attached) Acute hearing loss Muscle pain

4. In view of above, progress report is placed before CSC for appraisal & request for extension in trial duration for another year as per NBC approval, please.

5. Submitted for consideration of CSC:

Decision:

*The CSC after detailed discussion and deliberation decided to grant extension in the duration of the Clinical Trial titled, "*Scynexis Protocol Number SCY-078-305, Open-Label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of SCY 078 (Ibrexafungerp) in Patients with Candidiasis Including Candidemia, Caused by Candida Auris. (CARES)*"", for another year, as approved by the National Bioethics Committee.*

Further the Committee showed its concerns regarding the extension in trial duration as perusal of progress report reflected that, the pace of the trial was very much slow. So, the PI should try hard to conclude the study within this extended period of time & that further extension in trial duration will not be allowed.

AGENDA ITEM XI:

MONTHLY PROGRESS REPORT OF ONGOING CLINICAL TRIAL/STUDY TITLED AS A GLOBAL, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III CLINICAL STUDY TO EVALUATE THE EFFICACY, SAFETY, AND IMMUNOGENICITY OF SEQUENTIAL IMMUNIZATION OF RECOMBINANT SARS-COV-2 FUSION PROTEIN VACCINE (V-01) AGAINST COVID-19 IN HEALTHY ADULTS AGED 18 YEARS AND OLDER AFTER THE VACCINATION OF 2 DOSES OF INACTIVATED VACCINES. F. No.03-74/2021 DD (PS).

Case is from M/s DRK Pharma Solutions, Lahore, wherein they have submitted the monthly progress report for ongoing Livzon, Study at six sites approved by CSC. The detail is as under: -

Sr No.	Name of Site	Total Subjects Screened	Total Subjects Randomized	Total Failures
1.	M/s Central Park Teaching Hospital, Lahore	1478	1351	16
2.	M/s Avicenna Medical & Dental College, Hospital, Lahore	1442	1318	30
3.	M/s Shifa International Hospital, Islamabad	1619	1568	48
4.	M/s Dow University of Health Sciences, Ojha Campus, Karachi	403	390	5
5.	M/s Sindh Infectious Diseases Hospital and Research Centre, Karachi	509	500	0
6.	M/s Agha Khan University Hospital, Karachi.	291	259	7
Total		5742	5386	106

02. Submitted for consideration of CSC:

Decision:

The CSC after review of the submitted progress report was of the view point that, number of subjects enrolled at the six sites are not mentioned in the report & that, it also not reflects the SAEs observed/reported at the sites.

The Committee therefore directed the applicant/PIs to furnish the progress report as per ICH-GCP Guidelines & the Conduct of Clinical Trial Guidelines issued by the Division of Pharmacy Services, DRAP.

AGENDA ITEM XII:

APPLICATION FOR THE INCREASE IN RECRUITMENT OF CLINICAL TRIAL SUBJECTS AND FOR IMPORT OF ADDITIONAL 6000 DOSES FOR ONGOING CLINICAL TRIAL NAMED A GLOBAL, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III CLINICAL STUDY TO EVALUATE THE EFFICACY, SAFETY, AND IMMUNOGENICITY OF SEQUENTIAL IMMUNIZATION OF RECOMBINANT SARS-COV-2 FUSION PROTEIN VACCINE (V-01) AGAINST COVID-19 IN HEALTHY ADULTS AGED 18 YEARS AND OLDER AFTER THE VACCINATION OF 2 DOSES OF INACTIVATED VACCINES. F. No.03-74/2021 DD (PS).

Application is from M/s DRK Pharma Solutions, Lahore wherein they have requested for the increase in recruitment of clinical trial subjects for ongoing Livzon study, initially they applied for 8,000 subjects, now they have requested for recruitment of 5000 more subjects and have also requested for import of additional 6000 doses (3000 placebo and 3000 IMPs). The previous permission was for the import of 9600 doses.

2. After evaluation of documents furnished, the applicant was advised to deposit amendment fee of Rs.25000 in DRAP head of account for processing their requests for amendment in ongoing study for additional recruitment of trial subjects and import of additional quantities of trial material as per amended trial/study protocol. The applicant was communicated the deficiencies vide letter dated 06th January 2021 to submit the following: -

i. Copy of amended protocol dully signed by the sponsor.
ii. Prescribed fee of Rs.25000/- as required under the Bio-Study Rules.

3. The applicant has submitted the prescribed fee of Rs.25000/- in DRAP head of account vide slip No. 2872913254 dated 07-01-2022 and further submitted that the request is only to increase the sample size. Therefore, there is no change in the already approved protocol (V1.1), as it does not affect the trial participant's safety and rights, data collection and integrity, study procedure, testing laboratory methods or study end points and also provided the statement of the sponsor.

4. Details of IMPs utilization is as under:

Consumable Accountability

Sr.No.	Medical Device	Total Quantity (No. of Pieces)	Quantity Used	Description
1	SST collection tubes	4,800	4,600	200
2	Cryogenic vials 1.5ml	12,000	10,500	1,500
3	Disposable pipette	2,400	2,000	400
4	Labels	16,800	16,800	0
5	Cryogenic box, 9*9	200	180	20
6	Biohazard Bags	200	150	50
7	Freezer Maker	7	7	0
8	Swab	1200	1200	0
9	VTM-N	800	800	0
10	Labels	800	800	0

IMP Accountability

Site. No	Hospital Name	Total Vaccine Shipped	Available at Site
9201	The Aga Khan University Hospital	1000	196
9202	Dow University Hospital	700	154
9203	Sindh Infectious Disease Hospital & Research Centre	800	141
9204	Shifa International Hospital	2100	97
9205	Avicenna Medical College and Hospital, Lahore	2100	159
9206	Al Khidmat Foundation- Surayya Azeem Waqf Hospital	200	200
9207	Central Hospital	200	200
9208	Central Park Medical College and Hospital	2100	41
Total		**9200**	**1188**

Total Vaccine Shipped in Pakistan =9,600
Shipped at Sites=9,200
Remaining at Sites=1,188
Total Currently available in Pakistan=1,588

5. Submitted for consideration of CSC:

Decision:

The CSC after detailed discussion and deliberation decided to constitute a panel of experts for surprise inspection of the trial site(s) to evaluate progress of the trial for the interim analysis of the study.

It was also decided to ask the applicant for provision of import documents of already permitted quantities of IMPs for the study, its distribution & utilization record from the trial sites, involved in the study, duly verified by the concerned PI/CRO.

AGENDA ITEM XIII:

SUBMISSION OF EXTENSION BY NBC IN ONGOING STUDY/TRIAL TITLED "A GLOBAL, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III CLINICAL STUDY TO EVALUATE THE EFFICACY, SAFETY, AND IMMUNOGENICITY OF SEQUENTIAL IMMUNIZATION OF RECOMBINANT SARS-COV-2 FUSION PROTEIN VACCINE (V-01) AGAINST COVID-19 IN HEALTHY ADULTS AGED 18 YEARS AND OLDER AFTER THE VACCINATION OF 2 DOSES OF INACTIVATED VACCINES". F. No.03-74/2021 DD (PS).

Application is from M/s DRK Pharma Solutions, Lahore, wherein the applicant has submitted the NBC approval for extension in ongoing study for six months.

2. It is submitted that the initial approval is for 6 months commencing from July 30th 2021 which expires on 30th January 2022, now after submission of NBC extension it is valid for additional six months i.e. 30th July 2022.

02. Submitted for consideration of CSC:

Decision:

The CSC was apprised regarding the extension in trial ethical approval issued by National Bioethics Committee for additional six months i.e. 30th July 2022. The committee was also apprised that, the trial under reference was approved by CSC for a period of 22 months.

AGENDA ITEM XIV:

ADDITION OF TWO NEWLY APPROVED SITES IN ALREADY ONGOING TRIAL NAMED A GLOBAL, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III CLINICAL STUDY TO EVALUATE THE EFFICACY, SAFETY, AND IMMUNOGENICITY OF SEQUENTIAL IMMUNIZATION OF RECOMBINANT SARS-COV-2 FUSION PROTEIN VACCINE (V-01) AGAINST COVID-19 IN HEALTHY ADULTS AGED 18 YEARS AND OLDER AFTER THE VACCINATION OF 2 DOSES OF INACTIVATED VACCINES F. No.03-74/2021 DD (PS).

The case is application from M/s DRK, Pharma Solutions, Lahore, wherein they have requested for addition of two sites i.e. M/s Surraya Azeem Teaching Hospital, Lahore and M/s Central Hospital Gujranwala.

2. It is submitted that after initial scrutiny shortcomings observed in the trial application were communicated to the applicant vide letter dated 23rd August 2021. The applicant was advised to submit applications on form -I for approval of remaining two un-approved clinical trial sites. As per directions of Chairman CSC the instant case for the consideration of study trial was placed before CSC in its 31st meeting held on 26th August, 2021, the decision of the CSC is as under:

"The CSC after deliberation / detailed discussion decided to defer the case till fulfilment of all prerequisites of the application as briefed by Secretary CSC &further review of the trail application by expert members of CSC as per international practices & WHO recommendations and in the light of safety data worldwide regarding mix & match vaccine trial/study".

3. The applicant submitted the data regarding safety in case and Dr Syed Faisal Mehmood, Associate professor, Principal Investigator of the trial joined the meeting in-person & briefed the committee regarding the safety of the trial as apprehended by CSC members during the previous

meeting. He also answered the questions raised by the members. The CSC members were satisfied with the presentation of the case by the PI. Asim Munir, Project Manager, M/s DRK, Pharma Solution, Lahore also furnished some documentary evidences with respect to mix and match trial studies carried out in different countries before the CSC in its 32nd Meeting held on 12th October, 2021. The decision of the CSC taken in the meeting is reproduced as under

"The CSC after deliberation / detailed discussion decided to approve the clinical trial tilled, "A Global, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Phase-III Clinical Study to Evaluate the Efficacy, Safety, and Immunogenicity of Sequential Immunization of Recombinant SARS-COV-2 Fusion Protein Vaccine (l/-01) Against COVID-19 in Healthy Adults Aged 18 Years and Older After the Vaccination of 2 Doses of Inactivated Vaccines".

4. Accordingly, registration letter of the study was issued on 27th October, 2021 for the subject trial/study mentioning the six sites already approved by CSC. Two sites M/s Surayya Azeem, Lahore and M/s Central Hospital Gujranwala were not approved by CSC till that date.

5. Applications for remaining sites were submitted by the applicants on 25th & 27th August 2021. After initial scrutiny of applications shortcomings were communicated to the applicants. The inspection panel for M/s Central Hospital, Gujranwala was constituted by the Chairman CSC on 6th September 2021 and letter was issued on 08-09-2021. The inspection panel for M/s Surraya Azeem Teaching Hospital, Lahore was constituted by the Chairman CSC on 20th October 2021 and inspection letter was issued on same date.

6. Both the sites were inspected by the panel of experts on 26-10-2021 & the reports were placed before the CSC in its 33rd meeting held on 11th November 2021. The CSC in the light of recommendation of the panel approved both the sites for Phase-III and Phase-IV clinical trials. Accordingly, the licenses bearing no. CTS 0080 & CTS 0081 for these sites to act as Clinical Trial Sites were issued on 17th November, 2021.

7. Now the applicant has submitted a request to initiate the recruitment of subjects in above said clinical trial/study at M/s Surraya Azeem Teaching Hospital, Lahore & M/s Central Hospital Gujranwala.

7. As per Form-VI i.e. Registration/approval to conduct the clinical trials / study, applicant is authorized to conduct the clinical trials or study on the sites as per provided details on the registration letter or in such other places as the approving authority may from time to time authorize.

8. As per Rule 7 of Bio-study Rules 2017, the application for the registration/approval of trial/study along with all the pre-requisites is submitted on Form-II. The application is scrutinized by the Division of Pharmacy Services and if required may be sent to experts appointed by DRAP for its evaluation. Once the application is thoroughly reviewed and evaluated by the concerned Desk Officer and finds that no further clarification or technical opinion of the expert is required, it shall be placed, with all the data, before the CSC in its very next meeting for consideration. The CSC after consideration of the case decides to approve or reject the application, keeping in view the public interest. Once approved, the Certificate of approval of clinical trial/registration letter is issued on Form-VI. Any change in registration letter is placed before CSC, if CSC approves the changes, the same will be communicated to the applicant.

9. In light above the case is placed for inclusion of two approved sites in already approved clinical study before approving authority i.e. Clinical Studies Committee (CSC).

10. Submitted for consideration of CSC:

11. The Secretary CSC apprised the Committee regarding the approval of the above said new trial sites after the approval of the study by the CSC & grant of registration letter of the study for already approved six sites as mentioned above.

Decision:

"The CSC after detailed discussion and deliberation acceded to the request of the applicant for inclusion of two sites namely M/s Surraya Azeem Teaching Hospital, Lahore & M/s Central Hospital Gujranwala and to allow the recruitment at these sites for the conduct of Clinical Trial titled, a Global, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Phase III Clinical Study to Evaluate The Efficacy, Safety, And Immunogenicity Of Sequential Immunization Of Recombinant Sars-Cov-2 Fusion Protein Vaccine (V-01) Against Covid-19 In Healthy Adults Aged 18 Years And Older After The Vaccination Of 2 Doses of Inactivated Vaccines".

AGENDA ITEM XV:

AMENDMENT IN ALREADY APPROVED CLINICAL TRIAL TITLED A PHASE III RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED CLINICAL TRIAL IN 18 YEARS OF AGE AND ABOVE TO DETERMINE THE SAFETY AND EFFICACY OF ZF2001, A RECOMBINANT NOVEL CORONA VACCINE (CHO CELL) FOR PREVENTION OF COVID-19.

Application is from M/s DRK, Pharma Solutions, Lahore, an amendment stating that vaccine could get a better protection effect 7 days after the completion of the third dose instead of waiting for the 14th days CDE n China suggested to change the clinical trial protocol to evaluate the efficacy of vaccine after 7 days and they have submitted the following documents: -

i. Amended version of protocol 1.3.
ii. IRB approvals of all the (8) sites.
iii. NBC approval.
iv. Prescribed fee of Rs.25000/.

2. The applicant has requested for the amendment of protocol from version 1.2 to version 1.3. Summary of amendments are as under:

Table of Protocol Revision Instructions (V1.2 to V1.3)

Project Title: A Randomized, Double-Blind, Placebo-Controlled Phase III Clinical Trial to Evaluate the Efficacy and Safety of Recombinant Novel Coronavirus Vaccine (CHO Cell) for the Prevention of COVID-19 in Subjects Aged 18 and Above

Protocol No.: LKM-2020-NCV-GJ01

Serial No.	Original (V1.2, May 12, 2021)	Revised (V1.3, Jun 12, 2021)	Revision Basis
Efficacy evaluation:			
1	**Efficacy evaluation:** The incidence rate and efficacy of any severity of COVID-9 of any severity 14 days after whole vaccination.	**Efficacy evaluation:** The incidence rate and efficacy of any severity of COVID-9 of any severity 7 days after whole vaccination.	According to the preliminary data, the sponsor believed that it could get a better protection effect 7 days after the completion of the third dose, without waiting for the 14th day. It is suggested to change the clinical trial protocol to

2	**Primary endpoints:** (1) The endpoint of efficacy study: The number of any severity of COVID-9 cases 14 days after whole vaccination.	**Primary endpoints:** (1) The endpoint of efficacy study: The number of any severity of COVID-9 cases 7 days after whole vaccination.	evaluate the efficacy of vaccine after the 7 days as it is approved by CDE in China.
3	**Secondary endpoints:** (1) The endpoint of efficacy study: a. The number of severe and severity above COVID-19 cases 14 days after whole vaccination; b. The number of COVID-19 cases of any severity in populations of different age group (18-59 years vs. 60 years and above) 14 days after whole vaccination.	**Secondary endpoints:** (1) The endpoint of efficacy study: a. The number of severe and severity above COVID-19 cases 7 days after whole vaccination; b. The number of COVID-19 cases of any severity in populations of different age group (18-59 years vs. 60 years and above) 7 days after whole vaccination.	
4	**Statistical analysis method:** The efficacy for any severity of COVID-19 diagnosed 14 days after full course of vaccination will be evaluated based on E-mFAS and PPS.	The efficacy for any severity of COVID-19 diagnosed 7 days after full course of vaccination will be evaluated based on E-mFAS and PPS.	

3. Submitted for consideration of CSC:

Decision:

"The CSC after detailed discussion and deliberation decided to approve the amended revised protocol V 1.3. of the already approved Clinical Trial titled, "A Phase III Randomized, Double Blind, Placebo Controlled Clinical Trial in 18 Years of Age and Above to Determine the Safety and Efficacy of ZF2001, A Recombinant Novel Corona Vaccine (CHO Cell) for Prevention of COVID-19".

AGENDA ITEM XVI:

APPLICATION FOR APPROVAL OF APPLICATION TO ACT AS CRO M/S NUMS, RAWALPINDI.

Case is an application from Brig Muhammad Azhar Shams, SI(M) (Retd), CNIC:37101-8831686-5, Registrar of M/S National University of Medical Sciences (NUMS), C/O Military Hospital, Abid Majeed Road, Rawalpindi, Pakistan. Wherein the request has been made to license with DRAP to act as Clinical Research Organization (CRO).

2. 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.	Attached
2	Prescribed fee challan	Photocopy provided, original required to be submitted
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).	Copy of National University of Medical Sciences attached.
4	Details of premises including layout plan of the site.	Just two room layout attached without proper work place distribution to justify operations being done as CRO.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Not applicable as applied for CRO.
6	Names and qualifications of the above sections along with their staff.	Details regarding CVs of minimum division/departments required to work as CRO is need to be submitted.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Not applicable as applied for CRO.
8	Undertaking on affidavit	Attached

3. In light of evaluations following are the deficiencies were communicated to the applicant vide letter dated 1st November 2021: -

i. Original fee challan, DRAP copy need to be submitted.
ii. Justification of operations being done as CRO is required as just two room layouts is attached without proper work place distribution for the different divisions of CRO.
iii. Details regarding minimum Divisions/departments required to work as CRO need to be submitted as per decision of CSC taken in its 2nd meeting.
iv. CVs of technical staff/officials employed by the applicant mentioning their assigned tasks should be furnished as the submitted information is proposed designated CRO personnel.

3. Applicant submitted /addressed all above-mentioned shortcoming which was communicated vide letter bearing even number dated 01st November 2021.

4. In view of above, it is proposed that inspection panel may be constituted by CSC, for verification of facilities available at the site of CRO.

5. Submitted for consideration of CSC:

Decision:

"The CSC after detailed discussion and deliberation decided constitute the following inspection panel for inspection for verification of facilities available at the site to act as CRO:

i. *Prof. Brig. (R), Muzammil Hassan Najmi, Professor of Pharmacology, Foundation University, Islamabad.*
ii. *Dr. Masud Ur Rehman, Director Pharmacy Services/Chairman CSC.*
iii. *Dr. Rizwana Chaudhry, Ex-HOD Gynecology Department, Holy Family Hospital, Rawalpindi.*

2. *The panel will furnish the inspection report for the consideration & decision by the CSC".*

AGENDA ITEM XVII:

REQUEST TO IMPORT ADDITIONAL QUANTITIES OF DEVICES IN ALREADY ONGOING TRIAL NAMED A GLOBAL, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III CLINICAL STUDY TO EVALUATE THE EFFICACY, SAFETY, AND IMMUNOGENICITY OF SEQUENTIAL IMMUNIZATION OF RECOMBINANT SARS-COV-2 FUSION PROTEIN VACCINE (V-01) AGAINST COVID-19 IN HEALTHY ADULTS AGED 18 YEARS AND OLDER AFTER THE VACCINATION OF 2 DOSES OF INACTIVATED VACCINES F. No.03-74/2021 DD (PS).

The case is from DRK Pharma Solutions, Lahore wherein they have requested for the import of following additional devices due to increase in number of subjects used in Clinical Trial as per detailed below:-

S.No.	Medical Device	Manufactured by	Total Quantity (No. of Pieces)	Total Quantity (Packages)	Description
1	SST collection tubes	BD	32 Packages (100 tubes/package)	3200	Blood sample collection
2	Cryogenic vials 1.5ml	Guangzhou Jet Bio	80 Packages (100 tubes/package)	8000	Serum storage
3	Disposable pipette	Zhejiang GongDong	16 Packages (100 tubes/package)	2,400	Blood sample collection
4	Labels	Custom made	16,800 pcs	1600	Sample labelling
5	Cryogenic box, 7*7	NA	10 Boxes	10	Sample storage
6	Cryogenic box, 9*9	Wange	150 Boxes	150	Sample storage
7	Biosafety Bag	Bomi	180 bags	180	Sample storage
8	Kit Packing bags, Plasitic	Teddylab	/	2100	Sample Storage

9	Swab	Citotest	/	500	Virus Sample Collection
10	VTM-N	Citotest	/	1000	Virus Sample Collection
10	Labels	Teddylab	12500 pcs	12500	Sample Labelling

2. Submitted for consideration of CSC:

Decision:

"The CSC after detailed discussion and deliberation decided to defer the case for review/verification of consumption report of already approved/imported/utilized quantities of the devices. The applicant shall be asked to furnish the import documents, distribution & utilization record of the already shipped quantities of the devices for the study under reference".

AGENDA ITEM XVIII:

APPLICATION OF IMPORT OF ADDITIONAL QUANTITIES OF RT PCR KITS IN ALREADY APPROVED CLINICAL TRIAL TITLED A PHASE III RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED CLINICAL TRIAL IN 18 YEARS OF AGE AND ABOVE TO DETERMINE THE SAFETY AND EFFICACY OF ZF2001, A RECOMBINANT NOVEL CORONA VACCINE (CHO CELL) FOR PREVENTION OF COVID-19.

The case is an application from M/s DRK Pharma Solutions, Lahore wherein they have requested for the import of additional quantities of RT-PCR Kits.

2. the applicant provided the justification for the import of additional quantities of kits as per design of protocol, if any participant catches the COVID-19 during the follow-up period of one year it will be tested with the imported kits to maintain the standardization in the trial.

3. Following are the quantities as requested by the applicant: -

Medical Device/Components	Manufactured by	Total Boxes	Test kit per Box	Total quantity
SARs COV-2 Nucleic Acid Detection Kit (RT-PCR)	Shanghai Fosun Long March Medical Sciences Co., Ltd	32	96	3072
Specimen Collection Swab	Jiangsu Jianyou Medical Technology Co., Ltd	16	200	3072

4. Submitted for consideration of CSC:

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for review/verification of consumption report of already approved/imported/utilized quantities of the kits, so as to avoid misuse potential of the kits & their wastage as well. The applicant shall also be asked to furnish the import documents, distribution & utilization record of the already shipped quantities of the kits for the study under reference.

AGENDA ITEM XIX:

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

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

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

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

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

S. No.	Document	Remarks
1	Application on prescribed form-IIA.	Application on Form – IIA is provided.
2	Prescribed processing fee	Processing fee of Rs.200000/- deposited vide challan number 1932889, dated 08th April 2021.
3	Name of Investigational Product (including all available names; trade,	Attached

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

17	Summary of the protocol or synopsis (Investigational Product)	Attached.
18	Adverse Event Reporting Form	Attached.
19	Name of the monitor or clinical research associate	Muhammad Ibrar Ahmad Khan (CV attached)
20	Evidence of registration in the country of origin (GMP certificate along with CoPP or Free sale certificate)	Copy of GMP Certificate for M/s Medisure Laboratories Pakistan (Pvt) Ltd, Karachi is attached. Whereas, GMP Certificate for M/s PT. ABBOTT Indonesia, Marketing Authorization holder (Imported & Distributed by): Abbot Laboratories, Philippines.is not provided.
21	Copy of registration letter if registered in Pakistan	Copy of registration letter for Rahmacin (Clarithromycin) 250mg/5ml Suspension M/s Medisure Laboratories Pakistan (Pvt) Ltd, Karachi is attached. Whereas, registration letter of Klaricid® (Clarithromycin) 250mg / 5ml Suspension of M/s Abbott Laboratories Pakistan is not provided.
22	The proposed label of investigational product	Attached.
23	Quantity of investigational product to be used in the study along with justification (Note: All the quantities of the each of investigational product should be procured from one single source)	Attached.
24	Undertaking on affidavit	Attached.

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

5. Applicant submitted reply as follows:

S.No.	Shortcomings	Reply
01	BA/BE Study Center approval letter copy is not attached.	Provided in attachment.
02	Registration letter & GMP Certificate of Klaricid® (Clarithromycin) 250mg / 5ml Suspension of M/s Abbott Laboratories Pakistan is not provided.	Please note that Bioequivalence study will be submitted to exporting countries regulatory authorities, currently sponsor has the intention to submit the Bioequivalence study Rahmacin suspension 250mg/5ml in FDA Philippines. As per FDA Philippines Reference product Klaricid (Clarithromycin) 250mg / 5ml Suspension should be registered and Marketed in Philippines, because of that product has been procured from the Philippines market. Therefore,

		it is difficult to obtain Registration letter & GMP certificate of M/s Abbott Laboratories Philippines.
03	Clarification regarding formulation is required, as formulation furnished is **Clarocin** Suspension 250mg/5ml (70ml), whereas investigational product to be tested is **Rahmacin** Dry Suspension 250mg/5ml.	Please note that both Clarocin Suspension Rahmacin 250mg/5ml dry 250mg/5ml has same formulation. Batch formulas are also attached Suspension for your reference. Also note that Clarocin Suspension 250mg/5ml is locally registered brand name whereas Rahmacin dry Suspension 250mg/5ml is an approved brand name for export.
04	Complete Registration letter need to be provided.	Provided in attachment.
05	Label of Reference product are not provided.	Provided in attachment.
06	Quantity of test & reference product according to dose(s) to be used in the study need to describe.	Provided in attachment.
07	Cost of the project is not described	Provided in attachment.

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

7. Submitted for consideration of CSC:

8. Dr. Sadia Asim the applicant/PI of the study & SM Zeeshan joined the meeting through Zoom & briefed the Committee regarding their application

Decision:

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

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

AGENDA ITEM XX:

SIX MONTHLY PROGRESS REPORT OF CLINICAL TRIAL TITLED "A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE-II CLINICAL TRIAL TO EVALUATE THE EFFICACY & SAFETY OF CBP-307 IN SUBJECTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS (UC)" & DESTRUCTION OF EXPIRED/UNUSED INVESTIGATIONAL MEDICINAL PRODUCTS. F.NO.03-59/2021 DD (PS).

Application is from Dr. Saeed Hamid (PI), Director, Clinical Trial Unit, Professor & Consultant Gastroenterologist, Aga Khan University Hospital, Karachi, dated 04th January 2022. Wherein FR is a 6 monthly progress report of subject Clinical Trial (UC CBP-307CN002) August-2021 to December-2021.

2. Study progress report is as follows:

i. Progress report:

Principal Investigator Name/Site No.	**Total Number of Subjects Screened**	**Total Number of Subjects Screen failed**	**Total Number of Subjects withdrew consent**	**Total Number of patients randomized**	**Serious Adverse Events** (Aug-2021 to Dec-2021)
Dr. Saeed Hamid /2125	11	04	01	06	No serious adverse event was reported.

ii. Protocol deviations:

Subject ID	**Visit ID**	**Deviation Description**	**Date of Deviation**	**Category**
2151001	Week 1 Day 5	On day 5, subject number2151001 has received medication from kit number 2A01545 (dispensed on day 1) instead of kit number 2B01780 (dispensed on day 5). The subject was dispensed two bottles from kit number 2401545 which contain 1 capsule/bottle (CBP-307 0.05m9 or Placebo). However, this does not change the required dosing regimen (i.e., subject should receive a cumulative dose of 0.1m9 or placebo on day 5) as kit number 2801780 contains 2 capsules/bottle (2 placebo capsules or 2 CBP-307 0.05mg capsules).	17 Aug 2021	Minor
2151002	Week 1 Day 5	On day 5, subject number 2151002 has received medication from kit number 2A01542 (dispensed on day 1) instead of kit number 2801783 (dispensed on day 5). The subject was dispensed two bottles from kit number 2A01542 which contains 1 capsule/bottle (CBP-307 0.05m9 or Placebo). However, this does not change the required dosing regimen (i.e., subject should receive a cumulative dose of 0.1 mg or placebo on day 5) as kit number 2801783 contains 2 capsules/bottle (2 placebo capsules or 2 CBP- 307 0.05m9 capsules).	17 Aug 2021	Minor
2151001	Week 4 Day 28	On Day 28, subject number 2151001 has received medication from kit number 2C04619 (dispensed on day 8) instead of kit number 2C04624 (dispensed on day 28). The same kit was used to dispensed take home medications and subject 2151001 continued to receive medication from previously dispensed kit till day 41. However, this does not change the dosing regimen as the required cumulative dose remains the same.	10 Sep 2027	Minor
2151002	Week 4 Day 28	On Day 28, subject number 2151002 has received medication from kit number 2C04623 (dispensed on day 8) instead of kit number 2C04627 (dispensed on day 28). The same kit was used to dispensed take home medications and subject 2151002 continued to receive medication from previously dispensed kit till day 41. However, this does not change the dosing regimen as the required cumulative dose remains the same	10 Sep 2021	Minor
2151001	Sub-Study 2 of Stage	Subject 2i51001 recently transitioned into stage 2 sub-study 2 and receiving open label treatment. The patient was enrolled on ICF v5. In the protocol, it says for these patients, the treatment will follow protocol v5, the study		

	2	staff misunderstood that visit procedures would also follow v5, so no HOLTER has been performed for subject 2151C01 during stage 2 titration period. However, all 12-lead ECG has been performed, and patient is well without any cardiac-related complaint.		

3. Further applicant/PI Dr. Saeed Hamid (PI), Director, Clinical Trial Unit, Aga Khan University Hospital, Karachi, submitted a request for incineration of expired/Unused Investigational Medicinal Products (IMPs), dated 04th January 2022.

4. Applicant/PI informed that, following quantities of IMPs of the subject trial need to be incinerated/destroyed:

i. Quantity of bottles imported: 363
ii. Quantity of bottles used: 32
iii. Quantity of bottles Expired: 184

5. It is submitted that, as per DRAP record following quantities of IMPs were allowed:

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

6. Applicant/PI haven't provided any record of import licenses issued, IMPs clearance & a miscellaneous fee for the application.

7. In view of above six-monthly report of the trial is placed before CSC. Further a panel may be constituted by the CSC for verification of above-mentioned IMPs quantities, supervision of destruction/incineration process & issuance of destruction certificate in accordance with ICH-GCP Guidelines & Conduct of Clinical Trial Guidelines.

8. Further applicant/PI may be directed to submit prescribed fee for miscellaneous request along with all record of import licenses & IMPs clearance from DRAP with complete utilization record. Moreover, PI may be directed to keep expired/unused IMPs in safe custody.

9. Submitted for consideration of CSC:

Decision:

"The CSC after detailed discussion and deliberation decided to delegate the power to the Chairman CSC, as was practiced previously for constitution of the inspection panel for the purpose of the destruction of the IMPs available at the trial sites as per SOPs provided by the Sponsor, the ICH-GCP Guidelines and the Conduct of the Clinical Trials guidelines issued by the Pharmacy Services Division DRAP.

Further, the CSC directed the applicant to provide import licenses, clearance record & furnish distribution & utilization record of the IMPs along with prescribed fee of Rs.25000/- for miscellaneous request as per the Bio-Study Rules 2017".

AGENDA ITEM XXI:

PROGRESS REPORT & PROTOCOL AMENDMENT APPLICATION OF CLINICAL TRIAL TITLED, "A PHASE-III, MATRIX DESIGN, PARTIALLY DOUBLE BLIND, RANDOMIZED STUDY OF THE EFFICACY AND SAFETY OF 50mg LONAFARNIB / 100mg RITONAVIR BID WITH & WITHOUT 180mcg PEG IFN-ALFA-2A FOR 48 WEEKS, COMPARED WITH PEG IFN-ALFA-2A MONOTHERAPY AND PLACEBO TREATMENT IN PATIENT CHRONICALLY INFECTED WITH HEPATITIS DELTA VIRUS BEING MAINTAINED ON ANTI-HBV NUCLEOS (T) IDE THERAPY (D-LIVR)". F.NO.03-08/2019 DD (PS).

Application for protocol amendment is from Dr. Saeed Hamid (PI) & Director, Clinical Trial Unit, Aga Khan University, Karachi, dated 04th January 2022, received on 10th January 2022. Wherein F.R. is a request for protocol amendment in subject clinical trial.

2. Applicant provided following documents:
   i. Amendment Protocol EIG-LN F-011 v.2.0- 22Sep 2021.
   ii. 2. LNF IB Ed 8.0 Final 21Jan21 redline since Ed 7.1 corrected
   iii. IB VS-Addendum-Eiger-with signature.
   iv. AKUH-IRB approval, dated 08th December 2021. (Page 2161/Corr.)
   v. NBC Approval, dated 23rd December 2021. (Page 2162/Corr.)

3. After initial evaluation following shortcomings observed:
   i. Applicant not provided prescribed fee of Rs.25000/- for protocol amendment.

4. In view of above, it is proposed that, shortcoming may be communicated to applicant & the application for amendment is placed before CSC for its consideration & decision, please.

5. Dr. Saeed Hamid joined the meeting through Zoom & presented the case before CSC.

Decision:

"The CSC after detailed discussion and deliberation acceded to the request of applicant regarding approval of amendments as per protocol EIG-LN F-011 v.2.0- 22nd Sep 2021 & LNF IB Ed 8.0 Final 21 Jan 21 etc., subject to submission of prescribed fee of Rs. 25000/- in miscellaneous head".

AGENDA ITEM XXII:

AMENDMENTS IN CLINICAL TRIAL TITLED, "A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, NON-INFERIORITY PHASE-II CLINICAL TRIAL ON THE EFFICACY & SAFETY OF HOUTOU JIANWEILING TABLET IN THE TREATMENT OF CHRONIC NON-ATROPIC GASTRITIS. F.No.03-19/2020 DD (PS)

Application was from Prof. Dr. Muhammad Raza Shah, General Manager, CBSCR, International Center for Chemical & Biological Sciences, University of Karachi, dated 18th September 2021, wherein FR is in reply of this Division letter bearing even number dated 08th September 2021.

2. It is submitted that, the subject application was placed before CSC in its 31st meeting held on 28th September 2021. The committee decided the case as follow:

The CSC after deliberation / detailed discussion decided to approve the change/transfer of Clinical Trial Site from the Indus Hospital Karachi to CBSCR-ICCBS, Karachi subject to submission of IRB & NBC approval along with revised/amended protocol. In case PI want to retain sites (i.e. The Indus Hospital, Karachi, DOW University of Health Sciences, Karachi & Civil Hospital Karachi, as source of trial subjects). So, MoUs/agreements with trial subjects source sites need to be provided along with IRB approval from each site.

3. Accordingly, applicant/PI submitted following documents:

i. IRB approval issued by IEC-ICCBS, University of Karachi, Karachi.
ii. NBC approval letter.
iii. Revised trial protocol with single Clinical Trial Site.

4. It is submitted that, before issuance of trial registration letter it was observed that, applicant has not submitted relevant information regarding Omeprazole (reference IMPs), so the applicant was informed in a meeting in the office of the Director Pharmacy Services, further informed telephonically to provide relevant information.

5. Applicant/PI, Prof. Dr. Muhammad Raza Shah, General Manager, CBSCR, International Center for Chemical & Biological Sciences, University of Karachi, on 02nd December 2021, submitted following documents:

i. Copy of Re-registration certificate of Omeprazole enteric coated Tablets, manufactured by M/s China National Pharmaceutical Industry Co, Ltd., Beijing, China.
ii. Copy of GMP Certificate of M/s China National Pharmaceutical Industry Co, Ltd., Beijing, China.

6. In view of above, it is proposed that, as applicant has not provided the CoPP for Omeprazole enteric coated Tablets, manufactured by M/s China National Pharmaceutical Industry Co, Ltd., Beijing, China. So, the matter may be placed before CSC for its consideration & decision.

Decision:

"The CSC after detailed discussion and deliberation decided to defer the case for submission of CoPP of reference product i.e. Omeprazole enteric coated Tablets, manufactured by M/s China National Pharmaceutical Industry Co, Ltd., Beijing, China, as the applicant provided re-registration certificate OF THE product instead of its CoPP".

AGENDA ITEM XXIII:

AN INTERNATIONAL RANDOMIZED TRIAL OF ADDITIONAL TREATMENTS FOR COVID-19 IN HOSPITALIZED PATIENTS WHO ARE ALL RECEIVING THE LOCAL STANDARD OF CARE. TRIAL SHORT TITLE: SOLIDARITY PLUS TRIAL.

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

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

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

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

3. After evaluation of your reply and documents/information furnished on the matter in response to this division letter dated 01st December, 2021, it is requested to submit application on Form-II as fresh application along with all pre-requisite as required under Bio-Study Rules, 2017 due to following reasons vide letter dated 6th January 2022.

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

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

iii. Protocol of the trial is completely changed.

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

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

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

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

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

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Fee	copy of fee challan slip No.256391126292 dated 11.01.2022.
3	Investigator Brochure (s)	SmPC attached instead of investigator Brochure.

4	Final protocol	Attached.
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	52 countries around the world in collaboration with WHO
7	Phase of trial.	Phase III
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Artesunate 850 vials Imatinib 600 Tablets Infliximab 160 vials
9	Site of the trial	Shaukat Khanum Memorial Cancer Hospital and research Center, Lahore. Pakistan Institute of Medical Sciences (PIMS) Islamabad. Shifa International Hospital, Islamabad. Agha Khan University Hospital AKUH, Karachi. Indus Hospital, Karachi.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB/ERC approval from Shaukat Khanum Memorial Cancer Hospital and research Center, Indus Hospital, Shifa International Hospital, as amended approval in solidarity trial (Solidarity plus) is attached. Protocol number is the same. Approval from Shaheed Zulfiqar Ali Bhutto medical university for Solidarity plus trial is attached. **Only the composition of IRB of SKCH&RC is attached.** **IRB approval of agha Khan hospital not attached.**
11	Approval of National Bio-ethics Committee (NBC)	**An international randomized trial of additional treatments for covid-19 in hospitalized patients who are all receiving the local standard of care". (Trial Acronym: Solidarity (covid-93)** is **a**ttached
12	CV's of the Investigators	CVs of Dr. Aun Raza, Dr. Faisal Sultan, Salma Muhammad Abbas, Dr. Shahzeb Khan, Dr. Naseem Akhtar, Dr. Ejaz A. Khan, Dr. Nosheen Yasir, Dr. Syed Faisal Mehmood, Dr. Samreen Sarfraz are attached.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	CoA & GMP certificate for Artisunate of IPCA Laboratory, India is attached. CoA & GMP certificate for Imatinib of Lec pharmaceutical, A Sandoz company, Poslovna is attached.

		CoA & GMP certificate for Infliximab of Jansen, Cilag AG, Switzerland is attached. **COPP or Free Sale Certificate not attached.**
14	Pre-clinical/clinical safety studies	Applicant submitted that its available in SmPC.
15	Summary of Protocol	Trial Standard Operating Procedure and appendix attached.
16	Summary of Investigator Brochure	SmPC attached
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Around 120 patients
19	Name of Monitors & Clinical Research Associate	Clinical Trial Unit of the University of Bern will conduct the global monitoring. Trial Steering Committee and its Executive group, WHO Trial center, Geneva and Global Data and Safety monitoring committee etc. will monitor.
20	Evidence of registration in country of origin.	SmPC attached.
21	Copy of registration letter (if registered in Pakistan)	IMPs are to be imported.
22	Sample of label of the investigational product / drug.	Label of Artesunate (Larinate) & Infliximab (KitNumb) is attached. Label of Imatinib is not Attached.
22	Duration of trial	One year
23	Undertaking on Stamp paper	Not provided.

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

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

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

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

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

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

10. Submitted for consideration of CSC:

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

Decision:

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

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

AGENDA ITEM XXIV:

REGULATORY APPROVAL FOR THE STUDY TITLED "CLUSTER RANDOMIZED-CONTROLLED STUDY OF HOME-BASED HEPATITIS-C, SELF-TESTING IN KARACHI, PAKISTAN", PROTOCOL NUMBER:ASD-05-002, F.NO.03-80/2021 DD (PS).

It is submitted that, application was received on 13th September 2021 & after initial scrutiny shortcomings were communicated to the applicant on 06th October 2021. Meanwhile, as discussed with Director Pharmacy Services, all the pending & under processing applications be placed before CSC. Accordingly, subject application was also placed before CSC in 32nd meeting held on 12th October 2021. Dr. Saeed Hamid (PI) joined the meeting & briefed the CSC member regarding the study. CSC after discussion & detailed deliberation decided the case as follows:

Decision of 32nd CSC meeting:

The CSC after deliberation / detailed discussion decided to approve the clinical trial titled "Cluster Randomized-Controlled Study of Home-Based Hepatitis-C, Self-Testing in Karachi, Pakistan", Protocol Number:Asd-05-002", subject to fulfillment of all identified prerequisites as per the Form-II of the Bio-Study Rules and communicated to the applicant.

2. Decision of the Committee communicated to the applicant vide letter bearing number F.No.16-32/2021 DD(PS) on 15th October 2021. Further as per CSC decision identified shortcomings again communicated vide letter bearing even number dated 04th November 2021.

3. Applicant submitted reply in reference to communicated shortcomings on 08th November 2021 & after evaluation of the reply recorded observations again communicated to the applicant on 29th November 2021.

4. Applicant again submitted reply received through courier on 08th December 2021. Wherein reply is in reference to this division letter bearing even number dated 29th November 2021.

5. Applicant submitted reply as follows;

S.No.	Shortcomings	Reply
01	Details regarding OraQuick HCV Testing Kit (Test Device) is provided, whereas testing device/kit which will be used as	Subjects who are in the controlled group will be directed to go to their nearby government facility for testing for Hepatitis C virus. This testing will be carried out as

	routine testing & comparison device & related documents (CoPP of IMPs/GMP Certificate of the manufacturer) or ISO certification if in practice in country of origin or clarification in this regard, need to be provided.	per the approved protocols of the Hepatitis control program of Sindh government. The objective of this study self-testing and will be compared to compliance with the instructions to go to the government facility for Hepatitis C testing. This study is therefore looking at the feasibility of Hepatitis C self-testing in the community and is not comparing the efficiency of Hepatitis C self-testing with the routine testing done through the government programs. Details regarding OraQuick HCV Testing Kit (Test Device) have already been provided to you, to compare compliance of subjects with the Hepatitis C. **(Page 620/Corr.**)
02	Memon Goth Hospital, Karachi is not approved by DRAP, so it can't be used in any part/procedure of the trial prior to approval of DRAP.	Clinical Trials Unit at the Aga Khan University Hospital will be the study site to conduct the study, as it is approved by DRAP already. **(Page 620/Corr.**)

5. As applicant clarified regarding sites of trial, objective, design of the trial and has fulfilled all the identified shortcomings/prerequisites as per decision of CSC. Hence, registration letter number CT-0038 has been issued.

6. Submitted for ratification & information of CSC.

Decision:

The CSC was apprised about the case & the Committee after being informed accordingly ratified the issuance of the registration certificate of the study to applicant.

AGENDA ITEM XXV:

APPLICATION FOR LICENSE OF CLINICAL RESEARCH ORGANIZATION (CRO) FOR PROMEDIX (PRIVATE) LIMITED, MULTAN. F. No.15-54/2022 DD (PS)

Application is from Mr. Muhammad Tahir, CEO, Promedix, Multan. Wherein they have requested for license for Clinical Research Organization for Promedix (Private) Multan.

2. Application on Form-I along with prescribed Fee Rs.300030 vide slip No. 77903404624 dated 27.12.2021 has been submitted.

3. The application evaluated according to pre-requisites as mentioned in Form-I of the Bio-Study Rules notified vide SRO 697(I)/2018, as following: -

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached

2	Prescribed fee challan	Attached.
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	FBR Taxpayer Registration Certificate and SECP Certificate of Incorporation are 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.	Following Functionality/ divisions has been given. 1- Medical Function to provide medical oversight and inputs, to develop protocol and related documents etc. 2- Regulatory Submission Team to prepare regulatory / bioethical committee required dossier, corresponds with regulatory persons, submit regular updates and seek approvals from the authorities. 3. Clinical operations - the team provide end - to - end services for clinical research from feasibilities till close - out visits. 4- Data Management the team design and ensure the data collection parameters, perform quality analysis, raise risk areas for focus and perform interim analysis to predict and track progress of the trial. 5- Biostatistics The team help to design and study end points parameters and its statistical significance, help in sample size calculation for particular protocol, perform analysis on results and predict data interpretation of the research in process. 6- Medical Writing - The team develops report , study updates , medical information and publication , safety updates in consultation with medical function team , interpret the results from data collected in the light of objectives of the protocol and prepare medical information for communication with different stakeholders. 7- Quality Assurance - This team is to ensure quality parameters are inherited with the performance of the team in all aspects. Services for quality assurance / audit for internal and external teams lies with this team. 8- IT Team catered services for software development according to protocol.

		development of eCRF, online regular engagement of team members, maintenance of electronic record keeping and e - archiving services are provided by the IT team. 9. Admin & finance - This team monitor, track and record day - to - day administrative and financial aspects of the organization. 10- Human Resources - This team is responsible for hiring of qualified HR for the CRO. It also engages team for their continuous development and look after hiring, firing and other HR related matters from day - to - day activities. 11- Training & Development - Development of required skills for the assigned tasks, co monitoring, regular training for the required services, their development and appraisal suggestion and improvement of week areas in consultation of HR and senior management is done by Training & Development Team
6	Names and qualifications of the above sections along with their staff.	The Name and CVs of each division lead has been submitted. - Medical function - Dr. Hafiz Muhammad Zia Ul Hassan 2- Regulatory Submission Team Dr. Muhammad Farooq 3- Clinical Operations- Dr. Ahmad Kamal (R.Ph. , Pharm - D) 4- Data Management and IT Team - Mr. Rehman Gull 5- Biostatistics - Mr. Arif Hussain 6. Medical Writing - Dr. Hafiz Muhammad Zia 7- Quality Assurance - Dr. Muhammad Farooq 8. Admin & Finance - Mr. Muhammad Tahir 9- Human Resources - Mr. Farooq Amjid 10. Training & Development - Dr. Ahmad Kamal (R.Ph. , Pharm - D)
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	E-Stamp attached.

4. In view of above, it is proposed that inspection panel may be constituted by CSC, for verification of facilities available at the site to carry out proposed Phase-IV Clinical Trial as per GCP guidelines.

5. Submitted for consideration of CSC.

Decision:

"The CSC after detailed discussion and deliberation decided to delegate the power to the Chairman CSC, as was practiced previously for constitution of the inspection panel in the case under reference. The CSC further decided that, panel members shall be informed at least five (05) days before inspection of the proposed site to act as CRO".

AGENDA ITEM XXVI:

APPLICATION FOR AMENDMENT IN END TB (EVALUATING NEWLY APPROVED DRUGS FOR MULTIDRUG-RESISTANT TB)CLINICAL TRIAL PROTOCOL FROM VERSION 3.3 TO 3.5.F. No.03-04/2019-DD (PS)

Application submitted by Dr. Naseem Salahuddin, Principal Investigator of endTB Clinical Trial, The Indus Hospital Karachi, wherein application is for approval of protocol amendment from trial protocol version 3.3 to 3.5. application is submitted with prescribed fee of Rs.25000/- submitted vide challan number 52983577193, dated 20th May 2021.

2. Summary of change is as follows: (**Annex-I**)

- *Protocol version has been changed from 3.3 to 3.5. Version date has been changed from 14 February 2019 to 15 December 2020.*
- *Administrative changes (addition of Vietnam as a study country, addition of sites in India, Kazakhstan and Pakistan, update of IRBs, lead investigators, site PIs and sites)*
- *Modification of the study duration and of the estimated time to complete enrollment.*
- *Change of birth control requirements to align with guidance from Clinical Trials Facilitation Group of European Medicines Agencies.*
- *Change of exclusion criteria (deletion of albumin and modification of QRS complex duration to > = 120msec)*
- *Added possibility to perform study procedures at participants' homes or through remote visits to reduce risks during the COVID-I9 outbreak.*
- *Clarification on participation in another trial.*
- *Possibility to use linked endTB-Q trial screening consent form and screening results for endTB*
- *Additional information about secondary linezolid dose randomization in randomization section.*
- *Update of experimental regimen dosing according to weight.*
- *Clarification on allowable screening sputum specimen's collection and tests*
- *Addition of SARS-CoV-2 infection and COVID-l9 as covariates in analysis.*
- *Clarification on informed consent process: any witness must be able to read and write.*
- *Addition of Week 104 endpoint to application of assessable population.*
- *Modification of exploratory objective time point for linezolid dose reduction strategies (Week 104 instead of Week 73)*
- *Minor editorial and typographical updates and corrections*
- *Extraction of "Statement of Compliance" and "Institutions / Site Principal Investigators and Study Sites" from document body into appendices 2 and 3, respectively.*
- *Addition of the scientific rationale to drop the albumin exclusion criterion.*
- *Update of publication, dissemination and access section*

3. After initial scrutiny following shortcomings forwarded to applicant on 30th September 2021:

i. Amendment application, SAEs reports & application for use of IMPs between endTB & endTB-Q trials are not signed in original by the PI.
ii. SAEs report still submitted in the name of IRD-IRB, which is Sponsor of the trial.
iii. M/s Indus Hospital & Health Network, Karachi is not utilizing the IRB of their Hospital.
iv. Complete composition of the IRB of the Indus Hospital & Health Network, Karachi is need to be submitted.

4. Technical documents (track change protocol, justification for changes & summary) shared with CSC members through email on 01st October 2021 for review & comments.

5. **Submitted for perusal, discussion and decision of CSC.**

6. Dr. Naseem Salahuddin, is the Principal Investigator of endTB Clinical Trial. So, before discussion she left the meeting due to conflict of interest & Dr. Sadia Ausim representative of PI & Sponsor joined the meeting through Zoom & briefed the Committee regarding amendments & answered the questions raised by the CSC members.

Decision:

The CSC after deliberation / detailed discussion decided to defer the case for fulfillment of the already identified prerequisites & submission of clarification already communicated to the applicant.

7. Applicant submitted requisite information, ssubmitted for consideration of CSC.

Decision:

The CSC after detailed discussion and deliberation acceded to the request of the applicant for the approval of the amended/revised protocol Version 3.5. of the already approved Clinical Trial titled, "End TB (Evaluating Newly Approved Drugs for Multidrug-Resistant Tb)Clinical Trial".

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

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