Minutes of the 11th CSC Meeting held on 20th May 2020.

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1. The 11th CSC Meeting was held on 20th May 2020 through Zoom under the chairmanship of Dr. Abdur Rashid, Director Pharmacy Services Division / Chairman (CSC). The meeting was held online through Zoom from the Committee Room, 4th Floor, Drug Regulatory Authority of Pakistan, Islamabad.

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

Sr. No.	**Name**	**Designation**
01	Dr. Abdur Rashid.	Chairman CSC / Director Pharmacy Services.
02	Dr. Masud Ur Rehman.	Secretary CSC / Additional Director, Pharmacy Services.

3. Following members attended the meeting online through Zoom:

01	Dr. Faiza Bashir.	Chairman, Pakistan Health Research Council or his nominee, Islamabad.
02	Ms. Salwa Ahsan.	Chief of Pharmacy, Shifa International Hospital, Islamabad. Member CSC.
03	Dr. Farhana Badar.	Biostatistician & Epidemiologist, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore. Member CSC.
04	Dr. Tayab Husnain.	Head of CEMB / CAMB, Lahore. Co-opted CSC Member, under the direction of Ministry of National Health Services Regulation & Coordination.
05	Prof. Dr. Niaz Ahmed Akhter	VC-UoP Lahore Co-opted Member.
06	Dr. Naseem Salahuddin.	Director Infectious Diseases Indus Hospital, Karachi Co-opted CSC Member, under the direction of Ministry of National Health Services Regulation & Coordination.
07	Dr. Aamir Jaffary	Sindh Institute of Urology & Transplantation (SIUT), Karachi Co-opted Member.
08	Prof: Dr. Mushtaq Ahmed	Professor of Cardiology, Bach Khan Medical College, Mardan, KPK Co-opted Member.

3. The Meeting started with the Holy Verses. Subsequently, Chairman, CSC welcomed the participants and accordingly briefed them about the necessity of holding this meeting in the era of COVID-19 pandemic. He briefed that after approval of trials on COVID-19, investigations are positively carried out across Pakistan. Chairman, CSC also thanked members for their participation online through zoom.

4. Secretary CSC, accordingly presented the agenda.

AGENDA ITEM - I: **CONFIRMATION OF THE MINUTES OF THE 9TH CLINICAL STUDIES COMMITTEE MEETING.**

1.1 Minutes of 10th CSC meeting are placed for confirmation & signature of CSC members.

1.2. Submitted for perusal, discussion and decision of CSC.

1.3. ***Decision of 11th CSC meeting:***

The CSC confirmed the minutes of 10th Meeting of Clinical Studies Committee (CSC) held on 8th April 2020.

AGENDA ITEM - II: **LICENSING & REGISTRATION OF CLINICAL TRIAL SITE & CLINICAL TRIALS / STUDIES IN RESPECT OF COVID-19.**

2.1) **REQUEST FOR APPROVAL OF Hayatabad Medical Complex, Peshawar COVID-19 CONVALESCENT PLASAMA. F. No.15-41/2020 DD (PS)**

2.1.1. Application is an application from Dr. Shahtaj Khan, Professor & Incharge Pathology Department, Hayatabad Medical Complex, Peshawar, dated 27th April 2020, wherein the application is in reference to approval of Clinical Trial titled "EXPERIMENTAL USE OF COVID-19 CONVALESCENT PLASAMA FOR THE PURPOSE OF PASSIVE IMMUNIZATION IN CURRENT COVID-19 PANDEMIC IN PAKISTAN IN 2020.", which was approved in 9th CSC meeting held on dated 8th April 2020 to be conducted at following trial sites:

i. National Institute of Blood Disease and Bone Marrow, Transplantation (NIBD), Karachi.
ii. Liaquat University of Medical and Health Sciences, Jamshoro.
iii. University of Health Sciences, Lahore.

2.1.2. Dr. Shahtaj Khan applying for Clinical Trial Site approval

2.1.3. It is submitted that application evaluated according pre-requisites as mentioned in Form-I & II of the Bio-Study Rules 2017, and following are details of evaluation.

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached.
2	Fee	Not attached (to be treated as per DRAP policy during COVID-19)
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).	Applied Site is a tertiary care Government Hospital.
4	Details of premises including layout plan of the site.	Pathology Department Hayatabad Medical Complex Peshawar
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	List of Equipment/ Machinery of Pathology department is attached
6	Names and qualifications of the above sections along with their staff.	Prof. Dr. Shahtaj Khan Prof. Dr. Khalid Khan Dr. Saiqa Zahoor Prof. Dr. Saeed-ur Rehman Dr. Ansa Kulsoom Rehman
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Hayatabad Medical complex is a 1250 bedded tertiary care hospital. It is the state of the art accident and emergency center, intensive care unit with 25 Ventilators. Cardiac care unit, three medical unit, 2 pediatric units

		and cardiology unit. Every unit by itself fully equipped with EEG machines, Defibrillators, crash cards etc to cope with any untoward reaction.
8	Undertaking on stamp paper	Attached.

2.1.4. Shortcoming were communicated to the applicant vide letter number F. No.15-41/2020 DD (PS), dated 6th May 2020.

2.1.5. Applied Site is a tertiary care government hospital.

2.1.6. Submitted for perusal, discussion and decision of CSC.

2.1.7. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation and owing to situation of COVID-19 pandemic in Pakistan in order to protect the patients, decided to approve the clinical trial site, to conduct already approved clinical trial titled "Experimental use of COVID-19 convalescent plasma for the purpose of passive immunization in current COVID-19 pandemic in Pakistan in 2020". It was also decided that the applicant meanwhile submit prerequisites as per the Bio-Study Rules 2017 as soon as possible.

Investigators will follow latest international protocols & guidelines issued regarding COVID-19 Clinical Studies. All applicants ensure prompt system of Pharmacovigilance and submit ADRs to DRAP, to ensure the safety of trial subjects.

2.2) LICENCE TO ACT AS CLINICAL TRIAL SITE AT SHAHEED ZULFIQAR ALI BHUTTO MEDICAL UNIVERSITY, ISLAMABAD. F. No.15-40/2020 DD (PS).

2.2.1. Application is from Prof. Tanwir Khaliq, Vice Chancellor, Shaheed Zulfiqar Ali Bhutto Medical University, Sector G-8/3, Islamabad, on dated 27th April, 2020. Wherein the request has been made to license their University with DRAP to act as CRO, Clinical Trial Site, BA / BE Center. Furthermore on 06-05-2020 team of representatives from PIMS visited Director Pharmacy Services and agreed to proceed the above said application for Clinical Trial Site only. Applicant applied subject mentioned licenses on Form-I of the Bio-Study Rules 2017.

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

i) Prescribed fee for approval of Clinical Trial Site need to be deposited.

ii) Details of premises including layout plan of the site need to be provided.

2.2.3. Shortcoming communicated to the applicant vide letter number F. No.15-40/2020 DD (PS), dated 6th May 2020, bet response is yet awaited.

2.2.4. Applied Site is a tertiary care government hospital, center applied for approval to conduct PROTECT Clinical Trial.

2.2.5. Submitted for perusal discussion and decision of CSC.

2.2.6. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation and owing to situation of COVID-19 pandemic in Pakistan in order to protect the patients, decided to approve the clinical trial site, to conduct already approved clinical trial titled "Hydroxychloroquine, Oseltamivir and Azithromycin for the treatment of COVID-19". It was also decided that the applicant meanwhile submit prerequisites as per the Bio-Study Rules 2017 as soon as possible.

Investigators will follow latest international protocols & guidelines issued regarding COVID-19 Clinical Studies. All applicants ensure prompt system of Pharmacovigilance and submit ADRs to DRAP, to ensure the safety of trial subjects.

2.3) EFFICACY OF INTRAVENOUS INFUSIONS OF STEM CELLS IN THE TREATMENT OF COVID-19 PATIENTS. F. No. 03-30/2020-DD (PS)

2.3.1. Application is vide reference No. 8041/JB&RSC dated 30.04.2020 received from Prof. Moazzam Nazeer Tarar, Chief Executive, Jinnah Burn & Reconstructive Surgery Centre, AIMS, Lahore with request for approval of CSC to carry out the captioned study in Jinnah Hospital. All needed information together with consent form in Urdu is presented in the closed application for kind consideration and approval by the committee. It is confirmed that the proposed study have approval of the institutional ethical review board as well as the institutional stem cell research and application committee.

2.3.2. As you will notice that the matter deal with current Corona epidemic therefore, the application may kindly be treated on priority basis and approval may be granted on compassionate grounds in the current emergent situation so that the work may start without delay.

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

i) Application is not on prescribed Form-II of the Bio-Study Rules2017.
ii) Prescribed fee for approval of the Clinical Trial is not provided.
iii) Investigator Brochure along with its summary are needed to be provided.
iv) Informed consent and participant information sheet only attached in Urdu, consent form in English is need to be submitted.
v) Institutional Review Board (IRB) approval of sites with complete composition of committee is need to be provided.
vi) Approval of National Bio-ethics Committee (NBC) is need to be provided.

vii) CV's of the Investigators are needed to be provided.
viii) Pre-clinical/clinical safety studies are needed to be provided.
ix) Adverse Event Reporting Form is need to be provided.
x) Number of Subjects/patients to be enrolled in each center/study needed to be described.
xi) Sample of label of the investigational product / drug is need to be provided.
xii) Duration of trial need to be described.
xiii) Undertaking on stamp paper is not provided.

2.3.4. Shortcoming communicated to the applicant vide letter number F. No.15-41/2020 DD (PS), dated 7th May 2020, bet response is yet awaited. Meanwhile, we may seek expert opinion from Biological Division on safety, efficacy and production techniques of stem cells.
2.3.5. Applied Site is a tertiary care government hospital.

2.3.6. Submitted for perusal discussion and decision of CSC.

2.3.7. Decision of 11th CSC meeting:

The CSC after detailed deliberation decided to forward to sub-committee of stem cells chaired by Prof. Dr. Riazuddin Sheikh, constituted under direction of Supreme Court for expert opinion. Report on the case will be presented before next CSC meeting

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2.4) REQUEST FOR APPROVAL FOR CENTRE, RAWALPINDI MEDICAL UNIVERSITY, RAWALPINDI, F. No. 15-42/2020 DD (PS)

2.4.1 Application from Professor Muhammad Umar, Vice Chancellor, Rawalpindi Medical University, Rawalpindi, dated 04th May 2020, wherein the application is in reference to approval of Clinical Trial titled Clinical Trial titled "APPROVAL FOR CENTRE." For clinical study "EXPERIMENTAL USE OF COVID-19 CONVALESCENT PLASAMA FOR THE PURPOSE OF PASSIVE IMMUNIZATION IN CURRENT COVID-19 PANDEMIC IN PAKISTAN IN 2020." which was approved in 9th CSC meeting.

2.4.2. Application evaluated according pre-requisites as mentioned in Form-I of the Bio-Study Rules 2017, and following shortcoming observed:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached. (Two trial sites applied on same Form-1)
2	Fee	Not Attached. (to be treated as per DRAP policy during COVID-19)
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the	**Holy Family hospital** & **Benazir Bhutto**

	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).	**Hospital** Both are Government tertiary care hospital.
4	Details of premises including layout plan of the site.	Both are Government tertiary care hospital.
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Enhancement of patient Care Equipment given instead of section wise list. List of hematology, pathology, Blood Bank and PCR Lab Equipment provided but hospital name not mentioned in this list.
6	Names and qualifications of the above sections along with their staff.	List of 15 Doctors Attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Not Submitted
8	Undertaking on stamp paper	Attached

2.4.3. Applied Site is a tertiary care government hospital.

2.4.4. Submitted for perusal discussion and decision of CSC.

2.4.5. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation and owing to situation of COVID-19 pandemic in Pakistan, decided to approve the clinical trial site, to conduct already approved clinical trial titled "Experimental use of convalescent plasma for the purpose of passive immunization". It was also decided that the applicant meanwhile submit prerequisites as per the Bio-Study Rules 2017 as soon as possible.

Principle Investigators will follow latest international protocols & guidelines issued regarding COVID-19 Clinical Studies. All applicants ensure prompt system of Pharmacovigilance and submit ADRs to DRAP, to ensure the safety of trial subjects.

2.5) <u>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 PUBLIC HEALTH EMERGENCY CLINICAL TRIAL. F. No.03-32/2020-DD (PS).</u>

2.5.1. Application is from Dr. Aun Raza consultant physician infectious diseases of M/s Shaukat Khanum Memorial Cancer Hospital and research Center, Lahore, dated 13th May 2020, wherein he has applied for approval or 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 public health emergency clinical trial."**

2.5.2. The primary objective of this large international randomized trial is to provide reliable estimates on any effect of these anti-viral treatments on in-hospital mortality in moderate and in severe COVID.

2.5.3. 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	Not provided. To be treated as per DRAP policy During COVID-19
3	Investigator Brochure (s)	Attached.
4	Final protocol	Attached.
5	Informed consent and participant information sheet (Urdu to English)	Attached
6	List of participating countries	Argentina, Brazil, Canada, Germany, Indonesia, Iran, Norway, Peru, Qatar, South Africa, Spain, Switzerland, Thailand.
7	Phase of trial.	Phase 3
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for	Chloroquine and Hydroxychloroquine—3000 to 4000 Remdesivir 3000 Lopinavir and ritonavir 14,000 to

	import of trial material.	15000 Interferon beta 250 to 300
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. Clinical Trial Sites are not approved for this study.
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, PIMS, Indus Hospital, Shifa International Hospital, Aga Khan University is attached.
11	Approval of National Bio-ethics Committee (NBC)	Attached
12	CV's of the Investigators	Attached
13	GMP certificate along with COPP & free sale certificate of the investigational product.	CoA attached. GMP certificate not attached except CIPLA Ltd.
14	Pre-clinical/clinical safety studies	Given in Investigator Brochure
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	In investigator brochure for Remdesivir.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	1000-1500
19	Name of Monitors & Clinical Research Associate	WHO R & D blueprint unit in Geneva, Switzerland Patrick Lydon

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.	Attached for one product
22	Duration of trial	Not provided.
23	Undertaking on Stamp paper	Not provided.

2.5.4. 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.

2.5.5. Who has established a global liability insurance (for individuals suffering serious adverse reactions arising from the use of investigational therapeutics for COVID-19 as part of Solidarity Trial) that will cover all the countries that participate in trial. This insurance mechanism to compensate individuals suffering from serious adverse reactions arising from the use of study drugs.

2.5.6. Submitted for perusal discussion and decision of CSC.

2.5.7. Decision of 11th CSC meeting:

The CSC after detailed deliberation and owing to situation of COVID-19 pandemic in Pakistan in order to protect the patients, decided to approve the clinical trial with title "Solidarity Public Health Emergency Clinical Trial".

Five trial sites are also approved as follows:

i. Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.
ii. Pakistan Institute of Medical Sciences (PIMS) Islamabad,
iii. Shifa International Hospital, Islamabad.
iv. Agha Khan University Hospital AKUH, Karachi.
v. Indus Hospital, Karachi.

It was also decided that same brand of Investigational Medicinal Products will be utilized at all trial site for locally manufactured drugs. Quantities mentioned in the application also allowed to import for the trial. The applicant meanwhile submit prerequisites as per the Bio-Study Rules 2017 as soon as possible.

Investigators will follow latest international protocols & guidelines issued regarding COVID-19 Clinical Studies. All applicants ensure prompt system of Pharmacovigilance and submit ADRs to DRAP, to ensure the safety of trial subjects.

2.6) REQUEST FOR APPROVAL FOR REGISTERATION OF CLINICAL TRIAL (F. No.15-43/2020 DD (PS)).

2.6.1. This Professor Muhammad Umar, Vice Chancellor, Rawalpindi Medical University, Rawalpindi, dated 11th May 2020, wherein the application is in reference to approval of Clinical Trial Site titled "APPROVAL FOR REGISTRATION OF CLINICAL TRIAL." For clinical study "PROTECT TRIAL:- HYDROXYCHLOROQUINE, OSELTAMIVIR AND AZITHROMYCIN FOR TREATMENT OF COVID-19 INFECTION".

2.6.2. Applicant has applied on both Form-I and Form-II. Although as per his covering letter he has applied for registration of Clinical trial (Protect trial) but protect trial is already approved in which principal investigator is Prof. Javaid Akram. Now as per Form-I it can be assumed that applicant wants approval of trial center. He has mentioned clinical trial sites as Hospitals attached with Rawalpindi Medical University. Application evaluated according pre-requisites as mentioned in Form-I of the Bio-Study Rules 2017, and following shortcoming observed:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Attached. RHU with allied hospital applied on same Form-1
2	Fee	Not Attached (to be decided as per policy during COVID-19).
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	RMU with its teaching hospitals recognized for undergraduate and post-graduate

	name and address of the company and its directors).	medical education under recognition of PMDC
4	Details of premises including layout plan of the site.	Not Submitted. Tertiary Care Hospitals
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	Not Attached.
6	Names and qualifications of the above sections along with their staff.	Not submitted.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Not provided.
8	Undertaking on stamp paper	Not provided.

2.6.3. RMU along with its allied hospitals have been applied on same Form-1 as Clinical trial sites for Protect Trial.

2.6.4. Submitted for perusal discussion and decision of CSC.

2.6.5. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation and owing to situation of COVID-19 pandemic in Pakistan in order to protect the patients, decided to approve the clinical trial site, to conduct already approved clinical trial titled "Hydroxychloroquine, Oseltamivir and Azithromycin for the treatment of COVID-19". It was also decided that the applicant meanwhile submit prerequisites as per the Bio-Study Rules 2017 as soon as possible.

Investigators will follow latest international protocols & guidelines issued regarding COVID-19 Clinical Studies. All applicants ensure prompt system of Pharmacovigilance and submit ADRs to DRAP, to ensure the safety of trial subjects.

2.7.) "A MULTICENTER, RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, PHASE-II CLINICAL TRIAL ON THE EFFECTIVENESS & SAFETY OF JINHUA QINGGAN GRANULES (JHQG) FOR THE TREATMENT OF COVID-19 PATIENTS".

2.7.1. Application is from Dr. Muhammad Raza Shah, General Manager, CBSCR, Dr. Panjwani Center for Molecular Medicine & Drug Research, International Center for Chemical & Biological Sciences, University of Karachi, dated 12th May 2020, wherein

request has been made for registration & approval of subject Clinical Trial, which will be carried out at DOW University Hospital, Karachi, Civil Hospital Karachi & other collaborative Hospitals. It is a Randomized, Double Blind, Placebo Controlled, Phase-II Clinical Trial, Application is on prescribed Form-II, without prescribed fee.

2.7.2. Study will be carried out under the supervision of Prof. Dr. Muhammad Raza Shah, by investigating CRO "Center for Bioequivalence & Clinical Research, International Center for Chemical & Biological Sciences, University of Karachi

2.7.3. The primary objective of the trial is to evaluate the efficacy and safety of Jinhua Qinggan Granules (JHQG) for the treatment of COVID-19 Patients.

2.7.4. Application scrutinized / evaluated according to pre-requisites as mentioned in Form-II of the Bio-Study Rules 2017, and status of the application is as follows:

i) National Bio-ethics Committee (NBC) & Institutional Review Board (IRB) approval from Clinical Trial sites are not provided.

ii) Described clinical trial sites as DOW University Hospital, Karachi. Civil Hospital Karachi, Other collaborative Hospitals are not approved from DRAP for subject Clinical trial.

iii) Attached COPP & Free Sale Certificate for the Investigational Medicinal Product (IMP) are in Chinese Can't be verified as verified/notified translation of certificates are not provided.

iv) Provided Labels of Investigational Medicinal Product (IMP) are not as per ICH-GCP guidelines.

2.7.5. Submitted for perusal discussion and decision of CSC.

2.7.6. ***Decision of 11th CSC meeting:***

The CSC discussed the trial protocol of TCM formulation i.e. Jinhua Qinggan Granules, submitted by ICCBS and asked the applicant for National Bioethics Committee (NBC) approval.

2.8) DEVELOPMENT OF DISPOSABLE VENTILATORS.

2.8.1. Application is from **Pakistan Association of Automotive parts & Accessories Manufacturer** to Pakistan Engineering Council and copied to 1) Maj. Gen. Aslam khan (R) Bahria International Hospital, Karachi, 2) Dr. Abdur Rashid, Director and Chairman, clinical Study committee-DRAP, Islamabad. Applicant has stated that Pakistan

Auto parts and accessories manufacturing association PAAPAN has under taken the development of PAAPAN vent-1 Ventilator assay to help and support the nation in current pandemic situation of |Covid-19. They have adopted and precisely reversed engineer the GO2Vent concept originated by M/s Votran Medical USA. This product is FDA approved and widely used globally including Pak Army since 2008. This product is highly user friendly in can be used as an ideal back up ventilator for the Natural disaster, disease outbreaks, Major power outages, rural health centers, dispensaries, Helicopter, Ambulance, Mobile Hospitals, etc. This Vent Assy has been developed by a group of experienced Auto Parts manufacturers for Japanese Car OEMS on production tooling; having a capacity of producing 500 assys/day. Their product is at final stage of internal testing and patient ready sample will be submitted till 13-May-2020. Mass production can be started within 10 days after approval by competent authorities. As a CSR initiative, PAAPAM will be offering initial 2,000, Ventilators Free of cost to NDMA and 8,000 Nos just on cost basis. They have attached the Tech specs, design parameters, Material data sheets, Operational Characteristics, User manual, as per guidelines of PEC-ATP-EM-PMVS 00:2020, including requirements of medical equipment manufacturing in compliance with ISO 13485:2016.

2.8.2. Applicant has further requested the support and guidance for the final testing and approval through your esteemed and approval through your esteemed platform and welcome any queries regarding design, manufacturing, assembly, testing and control at all stages.

2.8.3. applicant have attached Assembly view, Exploded view, user manual, vent design summary, component drawings, working parameters, competency training manual, user manual, comparison b/w ISO 13485 & INF IMS, summary of PEC-ATP, Xerox and vortan medical partnering, MSDS #E100 and KPN 1100 data sheet.

2.8.4. Regarding the approval of testing on ventilators on simulators, DRAP in its letter dated 13th April 2020 has informed that:-

i). No locally manufactured ventilator design/ prototype be processed by DRAP unless it is vetted/ validated by Pakistan Engineering Council (PEC).

ii). No ventilators shall be used on patients without prior approval of Experts Group on ventilators.

iii). Standards for Fast Track Acceptance Test Procedure for Locally Manufactured Mechanical Ventilators for ICU (Version 1.1) developed by

PEC and approved by Expert Group on Ventilators in Pakistan and the same has been uploaded on DRAP's website.

2.8.5. During the time required for the vetting/ validation by PEC, due to limited technical expertise, it is proposed that we may Co-opt member/ Expert under sub-rule 6 of rule 13 of Bio-Study Rules 2017, for technical evaluation of this file.

2.8.6. Submitted for perusal discussion and decision of CSC.

2.8.7. Decision of 11th CSC meeting:

The CSC after detailed deliberation and owing to situation of COVID-19 pandemic in Pakistan in order to protect the patients, decided to refer the case to Expert Committee on ventilators headed by Maj. Gen. Aslam Khan and get their opinion.

AGENDA ITEM - III: **LICENSING & REGISTRATION OF CLINICAL TRIAL SITE & CLINICAL STUDIES AND BIO-ANALYTICAL LABS UNDER THE BIO STUDY RULES, 2017.**

3.1) ULTIMATE-DAPT CLINICAL Trial to be conducted at Punjab Institute of Cardiology, Rawalpindi Institute of Cardiology & National Institute of Cardiology. F. No. 03-16/2019-DD (PS)

3.1.1. Application is from Prof. Dr. Saqib Shafi Sheikh, Chief Executive, PIC, Lahore, Principal Investigator, Punjab Institute of Cardiology, Lahore dated 18.11.2019 addressed to the Director, Pharmacy Services, DRAP, Islamabad. Wherein he stated that three centers from Pakistan have been selected for a very innovative Multi-Centre randomized trial that might change the international guideline. This would be a great honor for Pakistan.

3.1.2. Since the trial is ready to start in other countries and high volume centers in Pakistan can take a lead in trial subject to early participation. It is therefore requested to grant subject temporary registration of drug on fairly urgent basis so that leading role of Pakistan center is not jeopardized due to inordinate delay. Centers approved other than Punjab Institute of Cardiology (PIC) Lahore, for this trial are: Rawalpindi Institute of Cardiology (RIC) Rawalpindi and National Institute of Cardiovascular diseases (NICVD), Karachi.

3.1.3. This is a multicenter, randomized controlled research project titled "Comparison of 1-month versus Dual Antiplatelet Therapy after implantation of Drug-Eluting Stents Guided by either Intravascular Ultrasound or Angiography in Patients with Acute Coronary Syndrome" as per submitted documents by applicant, it is informed that the trial record is available on U.S National Trial Registry with identification number ***NCT03971500.***

3.1.4. Another application received from Dr. Muhammad Anjum, Study Coordinator, "ULTIMATE DAPT TRIALS", Punjab Institute of Cardiology, Lahore. For approval of subject trial, refer to pre paras, same application was already in process which was submitted by Prof. Dr. Saqib Shafi Sheikh, Chief Executive, PIC, Lahore, Principal Investigator, Punjab Institute of Cardiology, Lahore dated 18.11.2019, It is submitted that Dr. Asim Javaid, representative from Rawalpindi Institute of Cardiology, Rawalpindi. Application was evaluated as per Bio-Study Rules 2017 and shortcomings were communicated vide letter even number dated 3rd December 2019.

3.1.5. Meanwhile another reply received from Maj Gen (R) Dr. Azhar Mehmood Kayani, Executive Director, Rawalpindi Institute of cardiology, Rawalpindi in the name of CEO, DRAP, Islamabad in continuation to previously submitted application by Prof. Dr. Saqib Shafi Sheikh, Chief Executive, PIC, Lahore, Principal Investigator, Punjab Institute of Cardiology, Lahore dated 18.11.2019.

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

i. Original fee challan (DRAP Copy) endorsed by Budgets and accounts is required.
ii. Undertaking on stamp paper along with name, signature and seal of firm company required.

iii. Under S.RO. 1047AD019 it is necessary to submit Rs. 100,000/ fee through fee challan for each trial site along with relevant documents (Copy of S.RO. 1047AD019 attached).

3.1.7. Shortcomings communicated vide letter number F. No.03-16/2019 DD (PS), dated 7th May 2020.

3.1.8. Previously application was submitted by Prof. Dr. Saqib Shafi Sheikh, Chief Executive, PIC and now has been submitted by Maj Gen (R) Dr. Azhar Mehmood Kayani, Executive Director, Rawalpindi Institute of cardiology, Rawalpindi. Further applicant has requested CEO, DRAP to grant for the site Centres fee to help him to avoid unnecessary audit objection.

3.1.9. Submitted for perusal, discussion and decision of CSC.

3.1.10. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation withheld the case, it was also decided that study protocol will shared with Dr. Mushtaq Ahmed, Professor of Cardiology, Bach Khan Medical College, Mardan, KPK, Co-opted Member of CSC for his expert opinion, meanwhile applicant submit all prerequisites as per the Bio-Study Rules 2017 as soon as possible.

3.2) BIOEQUIVALENCE STUDY OF LAMNET (LAMOTRIGINE) 100MG TABLET OF M/S SEARLE COMPANY LTD BY ICCBS (Karachi University) F. No. 14-6/2018 DD (PS).

3.2.1. Application is from Dr. Muhammad Raza Shah, General Manager, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017.

3.2.2. The short summary of the proposed study is as under;

i. **Study title:** A Single Center, Open Label, Randomized, Single Dose, Two way Cross-over Study to explore the Bioequivalence Lamnet (Lamotrigine) 100mg Tablet with reference product Lamictal (Lamotrigine) 100mg Tablet under the fasting conditions in Healthy Male Pakistani Subjects.

ii. **Investigational Product:** Lamnet (Lamotrigine) 100mg Tablet of M/s Searle Company Ltd.

iii. **Reference Product:** Lamictal (Lamotrigine) 100mg Tablet of M/s GlaxoSmithKline Pakistan, Limited

iv. **Manufacturer:** M/s the Searle Company Limited, Karachi.

v. **Study Site:** Center for Bioequivalence Studies and Clinical Research (CBSCR), University of Karachi.

vi. **Principal Investigator:** Dr. Muhammad Raza Shah

vii. **Co-Principal Investigator:** Dr. Naghma Hashmi

3.2.3. Applicant fulfilled prerequisites as per Form-IIA of the Bio Study Rules 2017.

3.2.4. Submitted for perusal discussion and decision of CSC.

3.2.5. Prof. Dr. Raza Shah (P.I) also joined the meeting via zoom & presented the case before CSC and answered the question asked by the CSC members.

3.2.6. Decision of 11th CSC meeting:

The CSC after detailed deliberation decided to approve the BA/BE Studies for Lamnet (Lamotrigine) 100mg Tablet.

3.3) BIOEQUIVALENCE STUDY OF XORBAN (RIVAROXABEN) 20MG TABLET OF M/S SEARLE COMPANY LTD. BY ICCBS (Karachi University) F. No. 14-04/2018 DD (PS).

3.3.1 Application is from Dr. Muhammad Raza Shah, General Manager, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017.

3.3.2. The short summary of the proposed study is as under;

i. **Study title:** A Single Center, Open Label, Randomized, Single Dose, Two way Cross-over Study to explore the Bioequivalence Xorban (Rivaroxaben) 20mg Tablet with reference product Xarelto (Rivaroxaben) 20mg Tablet under the fasting conditions in Healthy Male Pakistani Subjects.

ii. **Investigational Product:** Xorban (Rivaroxaben) 20mg Tablet of M/s Searle Company Ltd.

iii. **Reference Product:** Xarelto (Rivaroxaben) 20mg Tablet of M/s GlaxoSmithKline Pakistan, Limited

iv. **Manufacturer:** M/s the Searle Company Limited, Karachi.

v. **Study Site:** Center for Bioequivalence Studies and Clinical Research (CBSCR), University of Karachi.

vi. **Principal Investigator:** Dr. Muhammad Raza Shah

vii. **Co-Principal Investigator:** Dr. Naghma Hashmi

3.3.3. Applicant fulfilled prerequisites as per Form-IIA of the Bio Study Rules 2017.

3.3.4. Submitted for perusal discussion and decision of CSC.

3.3.5. Prof. Dr. Raza Shah (P.I) also joined the meeting via zoom & presented the case before CSC and answered the question asked by the CSC members.

3.3.6. Decision of 11th CSC meeting:

The CSC after detailed deliberation decided to approve the BA/BE Studies for Xorban (Rivaroxaben) 20mg Tablet.

3.4) BIOEQUIVALENCE STUDY OF VAPTOR (ROSUVASTATIN) 20MG TABLET OF M/S SEARLE COMPANY LTD. BY ICCBS (Karachi University) F. No. 14-05/2018 DD (PS).

3.4.1. Application is from Dr. Muhammad Raza Shah, General Manager, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017.

3.4.2. The short summary of the proposed study is as under;

i. **Study title:** A Single Center, Open Label, Randomized, Single Dose, Two way Cross-over Study to explore the Bioequivalence Vaptor (Rosuvastatin) 20mg Tablet and Crestor (Rosuvastatin) 20mg Tablet under the fasting conditions in Healthy Male Pakistani Subjects.

ii. **Investigational Product:** Vaptor (Rosuvastatin) 20mg Tablet, manufactured by M/s **Searle** Company Limited, Karachi

iii. **Reference Product:** Crestor (Rosuvastatin) 20mg Tablet manufactured by **AstraZeneca.**

iv. **Manufacturer:** M/s the Searle Company Limited, Karachi.

v. **Study Site:** Center for Bioequivalence Studies and Clinical Research (CBSCR), University of Karachi.

vi. **Principal Investigator:** Dr. Muhammad Raza Shah

vii. **Co-Principal Investigator:** Dr. Naghma Hashmi.

3.4.3. Applicant fulfilled prerequisites as per Form-IIA of the Bio Study Rules 2017.

3.4.4. Submitted for perusal, discussion and decision of CSC.

3.4.5. Prof. Dr. Raza Shah (P.I) also joined the meeting via zoom & presented the case before CSC and answered the question asked by the CSC members.

3.4.6. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to approve the BA/BE Studies for Vaptor (Rosuvastatin) 20mg Tablet.

3.5) **REQUEST FOR THE APPROVAL "A SINGLE CENTER, OPEN LABEL, RANDOMIZED, SINGLE DOSE, TWO WAY CROSS-OVER STUDY TO EXPLORE THE BIOEQUVALANCE OF ANPLAG (TICAGRELOR) 90MG TABLETS (M/S PHARM EVO (PVT) LTD.) WITH THE REFERENCE PRODUCT BRILINTA 90 MG TABLET (M/S ASTRA ZENECA PHARMACEUTICALS, USA) UNDER FASTING CONDITIONS IN HEALTHY MALE PAKISTANI SUBJECTS".**

3.5.1. Application is from Dr. Muhammad Raza Shah, General Manager CBSCR, Dr. Panjwani Center for Molecular Medicine & Drug Research, International Center for Chemical & Biological Sciences, University of Karachi, dated 20th February 2020, wherein request has been made for registration & approval of subject Bio-Equivalence studies, application is on prescribed Form-IIA, along with a fee of Rs.200000/- deposited vide challan no.0813993.

3.5.2. The study carried out under the supervision of Dr. Muhammad Raza Shah (PI) & Dr. Naghma Hashmi (Co-PI), study sponsored by M/s Pharm Evo (Pvt) Ltd, Karachi & investigating CRO is CBSCR, International Center for Chemical & Biological Sciences, University of Karachi.

3.5.3. Sponsored by M/s Pharm Evo (Pvt) Ltd. About 44 volunteers will be enrolled for the study.

3.5.4. The short summary of the proposed study is as under;

i. **Study title:** A Single Center, Open Label, Randomized, Single Dose, Two Period, Two way Cross-over Study to explore the Bioequivalence Anplag (Ticagrelor) 90mg tablets (M/s Pharm Evo (Pvt) Ltd.) with the reference product Brilinta 90 mg tablet

(M/s Astra Zeneca Pharmaceuticals, USA) under the fasting conditions in Healthy Male Pakistani Subjects.

ii. **Investigational Product:** Anplag (Ticagrelor) 90mg tablets (M/s Pharm Evo (Pvt) Ltd.)

iii. **Reference Product:** Brilinta 90 mg tablet (M/s Astra Zeneca Pharmaceuticals, USA)

iv. **Manufacturer:** M/s Pharm Evo (Pvt) Ltd., Karachi.

v. **CRO and Study Site:** Center for Bioequivalence Studies and Clinical Research (CBSCR), University of Karachi.

vi. **Principal Investigator:** Dr. Muhammad Raza Shah

vii. **Co-Principal Investigator:** Dr. Naghma Hashmi

3.5.5. Applicant fulfilled prerequisites as per Form-IIA of the Bio Study Rules 2017.

3.5.6. Submitted for perusal discussion and decision of CSC.

3.5.7. Prof. Dr. Raza Shah (P.I) also joined the meeting via zoom & presented the case before CSC and answered the question asked by the CSC members.

3.5.8. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to approve the BA/BE Studies for Anplag (Ticagrelor) 90mg tablets.

3.6) REQUEST FOR APPROVAL & REGISTRATION OF "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.

3.6.1. Application is from Dr. Muhammad Raza Shah, General Manager, CBSCR, Dr. Panjwani Center for Molecular Medicine & Drug Research, International Center for Chemical & Biological Sciences, University of Karachi, dated 9th March 2020, wherein request has been made for registration & approval of subject Clinical Trial, which will be carried out at DOW University of Health Sciences, Karachi & the Indus Hospital, Karachi. It is a Randomized, Double Blind, Placebo Controlled, **Phase-II** Clinical Trial, Application is on prescribed Form-II, along with a fee of Rs.200000/- deposited vide challan no.0813994.

3.6.2. The study sponsored by Hunan Xinhui Pharmacy Co. Ltd, 18 Weilouke Road Wangcheng Economic Development Zone, Changsha City, Hunan Province, China. Study

will be carried out under the supervision of Prof. Dr. Muhammad Raza Shah, by investigating CRO "Center for Bioequivalence & Clinical Research, International Center for Chemical & Biological Sciences, University of Karachi

3.6.3. The primary objective of the trial is to evaluate the efficacy and safety of "Houtou Jianweiling Tablets" through the non-inferiority Clinical Trial of Houtou Jianweiling Tablets with Omeprazole Enteric-Coated Tablet in patients with chronic non-atrophic gastritis.

3.6.4. Application scrutinized / evaluated according to pre-requisites as mentioned in Form-II of the Bio-Study Rules 2017, and following documents & details found deficient in application:

i) National Bio-ethics Committee (NBC) & Institutional Review Board (IRB) approval from Clinical Trial sites.

ii) Clinical Trial Sites mentioned in the application (i.e. DOW University of Health Sciences, Karachi & the Indus Hospital, Karachi) are not approved for subject trail.

iii) Investigator Brochure & its summary as per ICH-GCP guidelines.

iv) Pre-clinical / clinical safety studies along with Phase-I results / report.

v) Provided Labels of Investigational Medicinal Product (IMP) are not as per ICH-GCP guidelines.

3.6.5. Submitted for perusal discussion and decision of CSC.

3.6.6. Prof. Dr. Raza Shah (P.I) also joined the meeting via zoom & presented the case before CSC and answered the question asked by the CSC members.

3.6.7. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation and decided to defer the case till ethical approval from NBC-PHRC & IRB/ERC.

3.7) PHARMACOKINETIC STUDY OF DEXTOP (DEXLANSOPRAZOLE) 60MG CAPSULES OF M/S SEARLE COMPANY LTD BY ICCBS.F. No.14-06/2018-DD (PS)

3.7.1. Application is from the General Manager, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017.

3.7.2. The short summary of the proposed study is as under;

i. **Study title:** A Single Center, Open Label, Randomized, Single Dose, One Period Study to explore the Pharmacokinetics of Dextop (Dexlansoprazole) 60mg Capsules under the fasting conditions in Healthy Male Pakistani Subjects.

ii. **Investigational Product:** Dextop (Dexlansoprazole) 60mg Capsules of M/s Searle Company Ltd.

iii. **Sponsor & Manufacturer:** M/s the Searle Company Limited, Karachi.

iv. **BA/BE Study Site:** Center for Bioequivalence Studies and Clinical Research (CBSCR), University of Karachi.

v. **Principal Investigator:** Dr. Muhammad Raza Shah

vi. **Co-Principal Investigator:** Dr. Naghma Hashmi

vii. **Funding Source**: The sponsor

3.7.3. Application was discussed in the 3rd Clinical Studies Committee (CSC) meeting, CSC decided as under:

Decision:

"The CSC after deliberations decided to defer the case till the approval of study site. The CSC also directed the applicant to remove the shortcomings".

3.7.4. Details of shortcomings are as under:

i) Only Rs.50000-/ submitted instead of prescribed fee of Rs.200000/- for approval of BA/BE Studies.
ii) Ethical approval from NBC-PHRC has not been provided.
iii) Undertaking on stamp paper is not provided.

3.7.5. Applicant repeatedly informed and directed for fulfilment of shortcomings by Division of Pharmacy Services, but applicant never responded, details of reminder is as follows:

i. Reminder-I sent on 09th March 2020.
ii. Reminder-II sent on 20th April 2020.
iii. Reminder-III sent on 07th May 2020.

3.7.6. Submitted for perusal, discussion and decision of CSC.

3.7.6. Prof. Dr. Raza Shah (P.I) also joined the meeting via zoom & presented the case before CSC and answered the question asked by the CSC members.

3.7.7 Decision of 11th CSC meeting:

The CSC after detailed deliberation, decided to defer the case till submission / fulfilment of all prerequisites as per the Bio-Study Rules 2017, till next CSC meeting.

3.8) BIOEQUIVALENCE STUDY OF MOKSI (MOXIFLOXACIN) 400MG TABLET. BY ICCBS. F. No.14-03/2018-DD (PS)

3.8.1. Application from the General Manager, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017.

3.8.2. The short summary of the proposed study is as under;

i. **Study title:** A Single Center, Open Label, Randomized, Single Dose, Two way Cross-over Study to explore the Relative Bioavailability of **Moksi (Moxifloxacin) 400mg Tablet** of M/s Abbott Laboratories and **Avelox (Moxifloxacin) 400mg Tablet** of M/s Bayer Pharmaceuticals under the fasting conditions in Healthy Male Pakistani Subjects.

ii. **Investigational Product:** Moksi (Moxifloxacin) 400mg Tablet

iii. **Reference Product:** Avelox (Moxifloxacin) 400mg Tablet of M/s Bayer Pharma

iv. **Sponsor & Manufacturer:** M/s Abbott Laboratories (Pakistan) Ltd., Karachi.

v. **BA/BE Study Site:** Center for Bioequivalence Studies and Clinical Research (CBSCR), University of Karachi.

vi. **Principal Investigator:** Dr. Muhammad Raza Shah

vii. **Co-Principal Investigator:** Dr. Naghma Hashmi

3.8.3. Application was discussed in the 3rd Clinical Studies Committee (CSC) meeting, CSC decided as under:

Decision:

"The CSC after deliberations decided to defer the case till the approval of study site. The CSC also directed the applicant to remove the shortcomings".

3.8.4. Details of shortcomings are as under:

i) Only Rs.50000-/ submitted instead of prescribed fee of Rs.200000/- for approval of BA/BE Studies.
ii) Ethical approval from NBC-PHRC has not been provided.
iii) Undertaking on stamp paper is not provided.

3.8.5. Applicant repeatedly informed and directed for fulfilment of shortcomings by Division of Pharmacy Services, but applicant never responded, details of reminder is as follows:

i. Reminder-I sent on 09th March 2020.

ii. Reminder-II sent on 20th April 2020.
iii. Reminder-III sent on 07th May 2020.

3.8.6. Submitted for perusal discussion and decision of CSC.

3.8.7. Prof. Dr. Raza Shah (P.I) also joined the meeting via zoom & presented the case before CSC and answered the question asked by the CSC members.

3.8.8. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation, rejected the application upon the request of applicant.

3.9) APPLICATION FOR APPROVAL AND REGISTRATION OF BIOEQUVALANCE STUDY OF *CLARITHRO*® TABLETS.

3.9.1. Application is from Prof. Dr. Tasneem Ahmed, CEO M/s Pharma Professional Services Pvt Ltd, PPS House Ettawah Cooperative Housing Society, Gadap Town, Near Gulshan-e-Maymar, Karachi, for approval of subject Bioequivalence Study, under the Bio-study rules, 2017, wherein the request has been made to register Bioequivalence studies, to determine the bioequivalence of test product **Clarithro® 500mg Tablets** manufactured by M/s Nabiqasim Industries (Pvt) Ltd, Karachi in health adult human subjects, compared with reference product **Klaricid® 500mg Tablets,** Manufactured by M/s Abbot Laboratories, Karachi.

3.9.2. The short summary of the proposed study is as under:

i. **Study title:** An open labelled Two period, Two Treatments, Two Sequences, Single Dose, Single Dose, Randomized, Crossover Bioequivalence Study Of Clarithromycin (Clarithro) 500mg Tablets in Healthy Volunteers, Compared to equivalent drug dose in reference formulation of KLARICID 500mg Tablets under fasting condition.
ii. **Investigational Product:** Clarithro® (Clarithromycin) 500mg Tablets of M/s Nabi Qasim (Pvt) Ltd
iii. **Reference Product:** Klaricid® (Clarithromycin) 500mg Tablets of M/s Abbott Laboratories, Karachi.
iv. **Sponsor & Manufacturer:** M/s Nabiqasim Industries (Pvt) Ltd, Karachi.
v. **CRO and Study Site:** M/s Pharma Professional Services (Pvt) Ltd, Karachi.
vi. **Principal Investigator:** Prof. Dr. Tasneem Ahmad
vii. **Funding Source**: The sponsor

3.9.3. Application was discussed in the 3rd Clinical Studies Committee (CSC) meeting, CSC decided as under:

Decision of 3rd CSC meeting:

"The CSC after deliberations decided to defer the case till the approval of study site. The CSC also directed the applicant to remove the shortcomings".

3.9.4. Details of shortcomings are as under:

i) Prescribed fee of Rs.200000/- for approval of BA/BE Studies is not provided.
ii) The approval of NBC-PHRC has not been provided yet.
iii) Undertaking on stamp paper is not provided.

3.9.5. Applicant repeatedly informed and directed for fulfilment of shortcomings by Division of Pharmacy Services, but applicant never responded, details of reminder is as follows:

i. Reminder-I sent on 09th March 2020.
ii. Reminder-II sent on 20th April 2020.
iii. Reminder-III sent on 07th May 2020.

3.9.6. Submitted for perusal discussion and decision of CSC.

3.9.7. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to reject the case.

3.10) APPLICATION FOR APPROVAL AND REGISTRATION OF COMPARATIVE CLINICAL STUDY OF IRPO-FA ® TABLETS.

3.10.1. Application is from Professor Dr. Tasneem Ahmed, CEO M/s Pharma Professional Services Pvt Ltd, PPS House A-93, Ettawah Cooperative Housing Society, Gadap Town, Near Gulshan-e-Maymar, Karachi, wherein request has been made to register a comparative clinical study to determine the efficacy and tolerability of combination tablets of Iron Polymaltose and Folic Acid of test product **Irpo-FA ® tablets** manufactured by M/s Nabiqasim Industries (PVT) Ltd, Karachi compared with reference product **Maltofer Fol® tablets,** manufactured under license of M/s (Vifor International) Inc, in woman with Iron deficiency Anaemia(IDA) including pregnant woman.

3.10.2. The short summary of the proposed study is as under;

i. **Study title:** A comparative, open labelled, multicentre, double arm, controlled, and randomized study in iron deficient anaemic women including pregnant woman to compare the efficacy and tolerability of test product Irpo-FA ® tablets manufactured by M/s Nabiqasim Industries (PVT) Ltd, Karachi with reference product Maltofer Fol® tablets, manufactured under license of M/s (Vifor International) Inc.

ii. **Investigational Product:** Irpo-FA ® (Iron Polymaltose and Folic Acid) tablets manufactured by M/s Nabiqasim Industries (PVT) Ltd, Karachi.

iii. **Reference Product:** Maltofer Fol® (Iron Polymaltose and Folic Acid) tablets**,** manufactured under license of M/s (Vifor International) Inc.

iv. **Manufacturer:** M/s Nabiqasim Industries (PVT) Ltd, Karachi**.**

v. **CRO:** M/s Pharma Professional Services (Pvt) Ltd, Karachi.

vi. **Study Sites:**

a. Department of Gynaecology, JPMC, Karachi;
b. Sobhraj Maternity Hospital Karachi; and
c. Karachi Medical Complex.

vii. **Principal Investigator:** Dr. Haleema Yasmin.

viii. Funding Source: The sponsor

3.10.3. Application was discussed in the 3rd Clinical Studies Committee (CSC) meeting, CSC decided as under:

Decision of 3rd CSC meeting:

"The CSC after deliberations decided to defer the case till the approval of study site. The CSC also directed the applicant to remove the shortcomings".

3.10.4. Details of shortcomings are as under:

i) Prescribed fee for approval of BA/BE Studies is not provided.
ii) The approval of NBC-PHRC has not been provided yet.
iii) The clinical trial sites of Department of obstetrics and Gynecology, JPMC, Karachi; Sobhraj Maternity Hospital Karachi; and Karachi Medical Complex are not licensed with DRAP neither the hospitals have applied for their license;
iv) The sites are not approved by the IRB/ethics committee; and
v) Undertaking on stamp paper is not provided.

3.10.5. Applicant repeatedly informed and directed for fulfilment of shortcomings by Division of Pharmacy Services, but applicant never responded, details of reminder is as follows:

i. Reminder-I sent on 09th March 2020.
ii. Reminder-II sent on 20th April 2020.
iii. Reminder-III sent on 07th May 2020.

3.10.6. Applicant in reference to this division reminder letter number F.No.14-10/2018 DD (PS) dated 20th April 2020 submitted withdrawal letter from subject application.

3.10.7. Submitted for perusal discussion and decision of CSC.

3.10.8. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to reject the case.

3.11) APPLICATION FOR APPROVAL AND REGISTRATION OF COMPARATIVE CLINICAL STUDY OF INJECTION MEGAFER.

3.11.1. Application is from Prof. Dr. Tasneem Ahmed, CEO M/s Pharma Professional Services Pvt Ltd, PPS House A-93, Ettawah Cooperative Housing Society, Gadap Town, Near Gulshan-e-Maymar, Karachi, wherein request has been made to register a comparative clinical study to determine the efficacy and safety of test product **Megafer Injection ®** manufactured by M/s Surge Laboratories (PVT) Ltd, Karachi, compared with reference product **Venofer Injection ®,** manufactured by M/s (Vifor International) Inc, in woman with Iron deficiency Anaemia (IDA).

3.11.2. The short summary of the proposed study is as under;

i. **Study title:** A comparative, open labelled, multicentre, parallel arm, controlled, and randomized study with 2 parallel groups to compare the efficacy and safety of test drug (Megafer Injection) with reference (Venofer Injection) in outpatient woman with Iron deficiency anaemia (IDA).
ii. **Investigational Product:** Megafer Injection ® (Iron Sucrose) manufactured by M/s Surge Laboratories (PVT) Ltd, Karachi.
iii. **Reference Product:** Venofer Injection ® (Iron Sucrose), manufactured by M/s (Vifor International) Inc.
iv. **Manufacturer:** M/s Surge Laboratories (PVT) Ltd, Karachi.
v. **CRO:** M/s Pharma Professional Services (Pvt) Ltd, Karachi.
vi. **Study Sites:**
    a. Department of Obstetrics and Gynaecology, JPMC, Karachi; and
    b. Sobhraj Maternity Hospital Karachi.
vii. **Principal Investigator:** Dr. Haleema Yasmin.

3.11.3. Application was discussed in the 3rd Clinical Studies Committee (CSC) meeting, CSC decided as under:

Decision of 3rd CSC meeting:

"The CSC after deliberations decided to defer the case till the approval of study site. The CSC also directed the applicant to remove the shortcomings".

3.11.4. Details of shortcomings are as under:

i) Prescribed fee for approval of BA/BE Studies is not provided.
ii) The approval of NBC-PHRC has not been provided yet.
iii) The clinical trial sites of Department of obstetrics and Gynecology, JPMC, Karachi; Sobhraj Maternity Hospital Karachi; and Karachi Medical Complex are not licensed with DRAP neither the hospitals have applied for their license.
iv) IRB /ethics review committee approval
v) Undertaking on stamp paper is not provided.

3.11.5. Applicant repeatedly informed and directed for fulfilment of shortcomings by Division of Pharmacy Services, but applicant never responded, details of reminder is as follows:

i. Reminder-I sent on 09th March 2020.
ii. Reminder-II sent on 20th April 2020.
iii. Reminder-III sent on 07th May 2020.
iv. 3.10.6. Applicant in reference to this division reminder letter number F.No.14-10/2018 DD (PS) dated 20th April 2020 submitted withdrawal letter from subject application.

3.11.6. Applicant in reference to this division reminder letter number F.No.14-11/2018 DD (PS) dated 20th April 2020 submitted withdrawal letter from subject application.

3.11.7. Submitted for perusal discussion and decision of CSC.

3.11.8. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to reject the case.

3.12) **APPLICATION FOR APPROVAL AND REGISTRATION OF COMPARATIVE CLINICAL STUDY OF *REXYL* ® COUGH SYRUP.**

3.12.1. Application is from Prof. Dr. Tasneem Ahmed, CEO M/s Pharma Professional Services Pvt Ltd, PPS House A-93, Ettawah Cooperative Housing Society, Gadap Town, Near Gulshan-e-Maymar, Karachi, wherein request has been made to register a comparative clinical study to determine the efficacy and safety of test product **Rexyl ® cough syrup** manufactured by M/s Nabiqasim Industries (Pvt) Ltd, Karachi, compared with reference product **Hydryllin ® cough syrup,** Manufactured by M/s The Searle Company Ltd in adult outpatients with productive cough.

3.12.2. The short summary of the proposed study is as under;

i. **Study title:** An open labelled, controlled, and randomized study with 2 parallel groups to compare the efficacy and safety of test drug (Rexyl cough syrup) with reference (Hydryllin cough syrup) in adult outpatients with productive cough.
ii. **Investigational Product:** Rexyl ® cough syrup (Aminophylline, Ammonium Chloride, Diphenhydramine and menthol), manufactured by Nabiqasim Industries (Pvt) limited, Karachi.
iii. **Reference Product:** Hydryllin ® cough syrup (Aminophylline, Ammonium Chloride, Diphenhydramine and Menthol) manufactured by the Searle Company Ltd.
iv. **Sponsor & Manufacturer:** M/s Nabiqasim Industries (Pvt) Ltd, Karachi.
v. **CRO:** M/s Pharma Professional Services (Pvt) Ltd, Karachi.
vi. **Study Site:** Karachi Medical Complex, Gulshan-e- Iqbal, Karachi.
vii. **Principal Investigator:** Prof Dr. M. Rafiq Khanani.

3.12.3. Application was discussed in the 3rd Clinical Studies Committee (CSC) meeting, CSC decided as under:

Decision of 3rd CSC meeting:

"The CSC after deliberations decided to defer the case till the approval of study site. The CSC also directed the applicant to remove the shortcomings".

3.12.4. It is submitted that application evaluated according pre-requisites as mentioned in Form-IIA of the Bio-Study Rules 2017, and following documents & details found deficient in application:

i) Prescribed fee for approval of BA/BE Studies.
ii) Ethical approval from NBC-PHRC.
iii) Clinical studies site, Karachi Medical Complex are not licensed with DRAP.

iv) IRB/ethics review committee approval

v) Undertaking on stamp paper.

3.12.5. Applicant repeatedly informed and directed for fulfilment of shortcomings by Division of Pharmacy Services, but applicant never responded, details of reminder is as follows:

i. Reminder-I sent on 09th March 2020.
ii. Reminder-II sent on 20th April 2020.
iii. Reminder-III sent on 07th May 2020.

3.12.6. Applicant in reference to this division reminder letter number F.No.14-12/2018 DD (PS) dated 20th April 2020 submitted withdrawal letter from subject application.

3.12.7. Submitted for perusal discussion and decision of CSC.

3.12.8. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to reject the case.

3.13) **OPEN LABEL, NON-RANDOMIZED, MULTI-CENTER INVESTIGATOR INITIATED STUDY TO EVALUATE EFFECTIVENESS OF GENERIC VELPATASVIR AND SOFOSBUVIR IN HEPATITIS-C WITH OR WITHOUT RIBAVIRIN AMONG PAKISTANI POPULATION F.No.3-3/2018 DD (P.S)**

3.13.1. Application is from Prof. Dr. Syed Muhammad Zahid Azam, Dow University Hospital, Karachi, wherein request has been made to for startup of subject clinical trial at following nine trial sites under the supervision of respective Investigators as mentioned against each;

S. No.	Trial Site	Name of Investigator
1	National Institute of Liver and G.I Diseases, Dow University of Health Sciences (Ojha Campus), Karachi	Prof. Dr. Syed Muhammad Zahid Azam
2	Gastrointestinal & Liver Practice & Research Center, DHA, Karachi	Prof. Dr. Syed Muhammad Zahid Azam
3	Liaquat National Hospital, Karachi	Asst. Prof. Dr. Sajjad Jamil
4	Shalamar Hospital, Lahore	Prof. Dr. Haroon Yousuf
5	Asian Institute of Medical Sciences, Hyderabad	Prof. Dr. Sadiq Memon
6	Gujranwala Gut & Liver Center, Gujranwala	Dr. Asad Chaudhary
7	Department of Medicine, Lady Reading Hospital, Peshawar	Prof. Dr. Javed Iqbal Farooqi
8	Al-Hayat Clinical & Research Center, Dabgari	Prof. Dr. Javed Iqbal

	Gardens, Peshawar	Farooqi
9	Quaid e Azam International Hospital, Islamabad	Associate Prof. Dr. Muhammad Salih

3.13.2. The purpose of this study as defined in the protocol, is to evaluate the effectiveness and safety of Velpatasvir/Sofosbuvir for the treatment of Chronic Hepatitis-C patients in Pakistani population and to assess the sustained virologic response at 12 weeks after the end of therapy.

3.13.3. Primary and secondary objective of the trial, as mentioned in the protocol (page 16/corr.), is as under;

i) Proportion of participants with sustained virologic response 12 weeks after discontinuation of therapy (SVR 12 weeks)

Secondary Objective:

i) Proportion of participants experiencing viral breakthrough (time frame: up to 12 weeks)
ii) Proportion of participants experiencing viral relapse (time frame: up to post-treatment week 12)
iii) Participants experiencing an adverse event leading to discontinuation of study medication (Time frame: Baseline to week 12).

3.13.4. It has been stated by the applicant that as it is an Investigator Initiated Study therefore they have requested M/s CCL Pharmaceuticals, Lahore to provide free of cost trial material and in response the company has agreed to provide the investigational material for 300 patients.

3.13.5. M/s CCL Pharmaceuticals, in their letter to the Principal Investigator, have admitted that currently they do not possess the registration of Sofosbuvir/Velpatasvir combination for marketing in Pakistan and their application is under process in Registration Division of DRAP, however they have been granted registration of this combination for "Export Purpose Only" from which they can provide the required quantity of drug for the said trial.

3.13.6. M/s CCL Pharmaceuticals, has also assured that they will not have any role in the conduct of this study, collection of data, monitoring, statistical analysis or data publication and they will not discuss any commercial aspect with investigators. However, their Senior Regulatory Affairs Manager, in a seminar on Pharmacovigilance in Lahore dated 12th May, 2018, has claimed that M/s CCL Pharmaceuticals is conducting this study with the help of Prof. Dr. Syed Muhammad Zahid Azam.

3.13.7. Perusal of submitted documents reveal that following pre-requisites need to be fulfilled by the applicant;

i) Product registered for "Export Purpose Only" cannot be utilized locally.

ii) Information regarding quantities and source of other trial material i.e Ribavirin has not been disclosed.
iii) Approval of National Bioethics Committee and IRB of study sites has not been furnished.
iv) Clarification from M/s CCL Pharmaceuticals regarding their direct involvement in the trial, as their Senior Regulatory Manager has claimed that the company is conducting this study.

3.13.8. In the view of above, the applicant may be asked to provide above mentioned missing information/documents and M/s CCL Pharmaceuticals may be asked to clarify their stance in relation to this trial, for further processing of the application.

3.13.9. It is submitted that the subject application was discussed in the 3rd CSC meeting & CSC decided as follows:

Decision of 3rd CSC meeting:

"The CSC after deliberations decided to defer the case till the approval of study site. The CSC also directed the applicant to remove the shortcomings".

3.13.10. Decision of the 3rd CSC meeting along with following shortcomings, communicated to applicant vide letter even number dated 8th July 2019, but no response yet received:

i) Only Rs.50000/- deposited instead of prescribed fee of Rs.200000/-, differential fee is not yet submitted instead of many reminders.
ii) Application for Clinical Trial Site approval on prescribed Form-I of the said rules and for approval of Clinical Studies to apply on prescribed Form-II.
iii) Product registration certificates used during Clinical studies not provided.
iv) Related to study title "Effectiveness of Generic Velpatasvir/Sofosbuvir…" license to manufacture drug for experimental purposes or drug registration certificate is required.
v) Complete information regarding quantities and source of Zovirin is required.
vi) GMP, CoPP and free sale certificate for the investigational products is required.
vii) Approval of National Bioethics Committee (PHRC) and Institutional Review Board of study sites is required.

3.13.11. In view of above applicant may directed to fulfill all prerequisites as per Form-IIA of the Bio-Study Rules 2017, within fortnight for further perusal of application, if agreed, DFA attached.

3.13.12. Applicant repeatedly informed and directed for fulfilment of shortcomings by Division of Pharmacy Services, but applicant never responded, details of reminder is as follows:

i. Reminder-I sent on 09th March 2020.
ii. Reminder-II sent on 20th April 2020.
iii. Reminder-III sent on 07th May 2020.

3.13.13. Submitted for perusal discussion and decision of CSC.

3.13.14. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to reject the case.

3.14) **SAFETY AND EFFICACY OF EMPAGLIFLOZIN (Diampa 10 & 20mg) IN PAKISTANI MUSLIM POPULATION WITH DIABETES MELLITUS BY M/S GETZ PHARMA (PVT) LTD. F. No.03-11/2019-DD (PS).**

3.14.1. Application is from Dr. Jahanzaib Kamal, Director Medical Affairs, Pharmacovigilance & Clinical Research, M/s Getz Pharma (Pvt) Ltd, dated 10th June, 2019, wherein request has been made for registration & approval of subject clinical trial, which will be carried out at following sites:

i) Habib Medical Center Dabgari Garden.
ii) National Institute of Cardiovascular Diseases Rafiqi H.J Shaheed Road, Karachi Cantonment, Karachi.
iii) Mahar Medical Center, Clifton, Karachi.
iv) Liaquat National Hospital, National Stadium Road Karachi.
v) Zubaida Medical Center Ghazi Slahuddin Road, C.P. Berar Society, Near Dhoraji Colony, Karachi.
vi) National Defense Hospital, Defence, Lahore.
vii) Diabetes Institute of Pakistan, Jail Road, Lahore.
viii) Jinnah Hospital, Usmani Road, Lahore.
ix) Al Khaliq Hospital, Nishtar Road, Multan.
x) Khattak Medical Center, Dora Road, Khattak Chowk, Shaheen Muslim Town, Peshawar, Khyber Pakhtoonkhwa.
xi) PIMS, G-8 Markaz, Islamabad.
xii) Shifa International Hospital, Pitras Bukhari Road, Islamabad.
xiii) Baluchistan Medical Center, Fatima Jinnah Road, Quetta.

3.14.2. Application is on prescribed Form-I, and along with a fee of Rs.50000/- deposited vide challan no.0785849, the study carried out under the supervision of Prof. Dr. Azizul Hassan Aamir, Head of Department of Diabetes and Endocrinology Postgraduate Medical Institute Hayatabad Medical Complex, Peshawar, Pakistan.

3.14.3. The primary objective of the trial is to compare the Safety & Efficacy of Empagliflozin versus other treatments in Pakistani Muslim population with type-II Diabetes Mellitus and funded by Getz Pharma.

3.14.4. The details of deficiencies is as under;

3.14.5. In the view of above following shortcomings are recorded:

i) Only Rs.50000/- deposited instead of prescribed fee of Rs.200000/-, differential fee is not yet submitted instead of many reminders.

ii) None of the following Clinical Trial Sites, as mentioned in trial application are approved from DRAP for applied clinical trial:

a. Habib Medical Center Dabgari Garden.
b. National Institute of Cardiovascular Diseases Rafiqi H.J Shaheed Road, Karachi Cantonment, Karachi.
c. Mahar Medical Center, Clifton, Karachi.
d. Liaquat National Hospital, National Stadium Road Karachi.
e. Zubaida Medical Center Ghazi Slahuddin Road, C.P. Berar Society, Near Dhoraji Colony, Karachi.
f. National Defense Hospital, Defence, Lahore.
g. Diabetes Institute of Pakistan, Jail Road, Lahore.
h. Jinnah Hospital, Usmani Road, Lahore.
i. Al Khaliq Hospital, Nishtar Road, Multan.
j. Khattak Medical Center, Dora Road, Khattak Chowk, Shaheen Muslim Town, Peshawar, Khyber Pakhtoonkhwa.
k. PIMS, G-8 Markaz, Islamabad.
l. Shifa International Hospital, Pitras Bukhari Road, Islamabad.
m. Baluchistan Medical Center, Fatima Jinnah Road, Quetta.

iii) Institutional Review Board (IRB) / Ethical Review Committee (ERC) approval of each sites with complete composition of committee is not provided.

iv) Approval from National Bio-ethics Committee (NBC) for the Clinical Trial is not provided.

v) Summary of Investigator Brochure is not provided.

vi) Details of patients to be enrolled in each center, is not provided.

vii) Undertaking on stamp paper is not provided.

3.14.6. Applicant repeatedly informed and directed for fulfilment of shortcomings by Division of Pharmacy Services, but applicant never responded, details of reminder is as follows:

i. Reminder-I sent on 09th March 2020.
ii. Reminder-II sent on 20th April 2020.
iii. Reminder-III sent on 07th May 2020.

3.14.7. Submitted for perusal discussion and decision of CSC.

3.14.8. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to defer the case till next CSC meeting, meanwhile applicant submit all prerequisites as per the Bio-Study Rules 2017 as soon as possible.

3.15) APPLICATION FOR AMENDMENT IN APPROVED PRPOTOCOL OF CLINICAL TRIAL "PREVENTION OF MATERNAL AND NEONATAL DEATH/INFECTIONS WITH A SINGLE ORAL DOSE OF AZITHROMYCIN IN WOMEN IN LABOR (IN LOW & MIDDLE INCOME COUNTRIES), A RANDOMIZED CONTROLLED TRIAL.

3.15.1 Application is from Prof. Dr. Sarah Saleem, Head of population & reproductive Health Unit, Department of Community Health Sciences, Aga Khan University, Karachi, dated 27th February 2020, to notify amendments in the registration certificate number **CT-0011**, for change in the study drug manufacturer & revised version of study protocol (version 1.4) for A-PLUS Clinical Trial".

3.15.2. Applicant informed following changes or amendments:

i. The study drug manufacturer is changed from ***LABORATORIOS CINFA, S.A.*** to ***KERN PHARMA S.L. Spain,*** whereas exporter of the drug (i.e ***IDIFARMA***) will remain the same.

ii. Based on the experience of pilot study, some minor amendments have been made in the protocol version 1.2 for which we have received the approval. New version 1.4 has some rephrasing of the operational definitions, secondary aims & study outcomes for clarity & consistency in the study tools.

3.15.3. Previously approved and amended agenda, both were also communicated to all CSC members for review by mail.

3.15.4. Applicant provided GMP Certificate for ***KERN PHARMA S.L. Spain*** & changed protocol version 1.4 along with tracked changes as well as clean copy of protocol version 1.4.

3.15.5. Summary of amendments (**Annex-I)**:

3.15.5. Submitted for perusal discussion and decision of CSC.

3.15.6. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to approve the amendments in already approved protocol by the CSC in its 6th meeting held on 20th January 2020. Amendments are described in the Annex-I of the agenda.

3.16) APPLICATION FOR AMENDMENT IN APPROVED PRPOTOCOL OF CLINICAL TRIAL TITLED "EVALUATING NEWLY APPROVED DRUGS FOR MULTIDRUG RESISTANT TB" (endTB) PHASE-III CLINICAL TRIAL.

3.16.1 Application is from Meherunissa Hamid, endTB Study Coordinator, The Indus Hospital Karachi, dated 29th April 2020, for minor administrative amendments made to the Protocol version 3.2 resulting in a new Protocol version 3.3. for endTB Clinical Trial.

3.16.2. Summary of Changes endTB v3.3 (Evaluating Newly approved Drugs for multidrug-resistant TB) **(Annex-II)**

3.16.3. Submitted for perusal discussion and decision of CSC.

3.16.4. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to approve the amendments in already approved protocol as per NBC approval, by the CSC in its 6th meeting held on 20th January 2020. Amendments are described in the Annex-II of the agenda.

3.17) REGULATORY APPROVAL FOR SCYNEXIS PROTOCOL NUMBER SCY-078-305, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SCY 078 (IBREXAFUNGERP) IN PATIENTS WITH CANDIDIASIS INCLUDING CANDIDEMIA, CAUSED BY CANDIDA AURIS. F. No.03-15/2019-DD (PS)

3.17.1 Application is from Dr. Faisal Mahmood, Associate Professor and Sec: Head Medicine, Aga Khan University, Karachi dated 08th October, 2019, wherein request has been made for registration & approval of subject clinical trial, which will be carried out at Aga

Khan University Hospital, Karachi. Application is on prescribed Form-II, along with a fee of Rs.200,000/- deposited vide challan no.1963578.

3.17.2. This is a multicenter, open-label, non-comparator, single-arm study to evaluate the efficacy, safety, tolerability and PK (pharmacokinetics) of oral SCY-078 as an emergency use treatment for patients with a documented Candida Auris infection as per available record on U.S National Trial Registry with identification number **NCT03363841** and as per the registry there are 5 locations globally, details of location is as follows:

United States, New Jersey

I. Scynexis, Inc. **Recruiting**
Jersey City, New Jersey, United States, 07302
Contact: David Angulo, MD 201-884-5471
david.angulo@scynexis.com

India

II. St John's Medical College and Hospital **Recruiting**
Bangalore, Karnataka, India, 560034
Contact: Alekya Vemula 8897752905 hemtrials.stjohns@sjri.res.in
Principal Investigator: Ross C Reuben, MD

III. Amrita Institute of Medical Sciences (AIMS) **Recruiting**
Kanayannur, Kochi, India, 682041
Contact: Puneet Dhar, MD 484-9447736769 pdhar@aims.amrita.cdu
Contact: Deepa Gijesh 484-9995184399 deepagijesh@aims.amrita.edu

IV. Institute of Critical Care Medicine Max Super Specialty Hospital **Recruiting**
Saket, New Delhi, India, 110017
Contact: Komal Handa 7888600688 Komal2@maxhealthcare.com
Principal Investigator: Deven Juneja, MD

V. Postgraduate Institute of Medical Education and Research, Department of Anaesthesia and special care **Recruiting**
Chandigarh, India, 160012
Contact: Narayana Yaddanapudi, MD 9815836656
narayana.yaddanapudi@gmail.com
Principal Investigator: Narayana Yaddanapudi, MD

3.17.3. The study carried out under the supervision of Dr. Faisal Mahmood (PI), along with Dr. Joveria Farooqi (Co-PI).

3.17.4. The trial comprises of following primary objective;

i. Efficacy as measured by the percentage of subjects with global success at end of treatment [Time Frame: Up to 90 days of study treatment]
Efficacy as measured by the percentage of subjects with global success (complete or partial global response) at EoT as determined by the Data Monitoring Committee

3.17.5. After evaluation following shortcoming & clarifications were recorded:

I. Kindly provide Sponsor's approval for nomination of M/s Metrics Research (Pvt) Ltd as CRO & following monitors for the trial:

i. Dr. Abdul Qaseem Khan, Sr. CRA. (Qaseem.khan@marco.com)
ii. Dr. Nazish Urooj, Sr. Manager. (drnazishi@marco.com)

II. Further as per trial application form & submitted protocol, it is stated that the trail is a Phase-III study, whereas study subject & sample size is not supporting the claim, so clarification is required.

3.17.6. Shortcomings were communicated through letter no. F.No.03-14/2019 DD (PS), dated 12th December 2019, but still response is awaited.

3.17.7. Dr. Sayed Faisal Mahmood, Associate Professor, Infectious Diseases, Aga Khan University Hospital, Karachi present before 6th CSC & briefed regarding the trial.

3.17.8. **Decision of 6thCSC Meeting: -**

"The CSC after deliberations deferred the case & decided to get experts opinion, because investigational drug is a new drug.

Applicant will be asked for trial data to be sent to the following experts for their opinion regarding the trail:

i) Dr. Faisal Sultan, Shaukat Khanum Memorial Hospital & Research Center, Lahore

ii) Dr. Javaid Bhutta, Shifa International Hospital, Islamabad.

iii) Dr. Sobia Qazi, Services Hospital, Lahore.

iv) Head of Department of Infectious Diseases Combined Military Hospital, (CMH), Rawalpindi.

Expert's opinion & recommendations will be presented before CSC in its next meeting."

3.17.9. Experts nominated by the CSC requested for their opinion on the trial through letter number F.No.03-15/2019, dated 27th February 2020, and a reminder also sent to Dr. Faisal Sultan & Dr. Javaid Bhutta on 20th April 2020.

3.17.10. **Dr. Sobia Qazi**, Associate Professor, Medical Unit-IV, SIMS / Services Hospital Lahore dated 18th March 2020, informed that, she had received & gone over the Protocol number SCY-078-305 of the subject clinical trial and had opinion that the subject trial may allowed. Whereas **Dr. Javaid Bhutta**, Shifa International Hospital, Islamabad**,** dated 29th April 2020, informed that, he had reviewed objectives & endpoints and found according to the standards and other aspects of the trial as Selection of Study Population, treatments, visits & efficacy and had opinion that the subject trial may be approved.

3.17.11. **Dr. Faisal Sultan,** Shaukat Khanum Memorial Hospital & Research Center, Lahore, dated 11th May 2020, informed that, he had reviewed the Study & recommend that subject trial may be approved.

3.17.12. Expert opinion from following experts is yet awaited:

i. ***Head of Department of Infectious Diseases Combined Military Hospital, (CMH), Rawalpindi.***

3.17.13. As there was no any official, the application could not be sent to them, only sent to above mentioned three evaluators/experts.

3.17.14. Submitted for perusal discussion and decision of CSC.

3.17.15. ***Decision of 11th CSC meeting:***

Based on the recommendations of experts & the CSC after detailed deliberation decided to approve the clinical studies titled "Protocol Number SCY-078-305, Open-Label Study to Evaluate the Efficacy, Safety, Tolerability and Pharmacokinetics of SCY 078-305 (IBREXAFUNGERP). In Patients with Candidiasis including Candidemia, Caused by Candida Auris".

3.18) APPLICATION FOR THE USE OF GRANULOCYTE COLONY STIMULATING FACTOR (GCSF) FOR BILIARY ATRESIA AS PART OF A PHASE-II CLINICAL TRIAL. F. No.03-10/2019-DD (PS)

3.18.1. Application is from Dr. Saqib Hamid Qazi, Assistant Professor & Head – Section of Pediatric Surgery, Director Pediatric Sugary Residency Program, Co-Chief – Children Hospital Service Line (Pediatric Surgery), Aga Khan University Hospital, Karachi, dated 16th May, 2019, wherein request has been made for registration & approval of subject clinical trial, which will be carried out at Aga Khan University Hospital, Stadium Road, Karachi.

3.18.2. The study carried out under the supervision of Dr. Saqib Qazi (P.I) and Dr. Abeer Aziz (Co-P.I), The primary objective is aim to assess the hypothesis that GCSF therapy improves the short term clinical outcome of biliary atresia in a multi institutional trial and to

prospectively evaluate, using the parameters mentioned within the study endpoints, the safety and efficacy of GCSF in each of two groups of newly diagnosed patients.

3.18.3. After evaluation of reply as per prerequisites of Form-II of the Bio-Study Rules 2017, following shortcoming observed;

i) Proof of authorization from Sponsor for the subject trial is not provided.
ii) Name & Contact details of Global Trial Lead & Sponsor of the subject trial.
iii) As per US Trial Registry the said trial is in early Phase-I and not completed yet, so how you can start Phase-II trial when Phase-I is in progress.
iv) Phase-I trial results are not provided.
v) Processing fee of Rs.100000/- is submitted whereas approved fee for Clinical Trial is Rs.200000/- as per S.R.O. 1047(I)/2019.
vi) As it is a multicounty trial so the source of medicine should be same for uniform results.
vii) Provided Investigator's Brochure is not as defined in ICH-GCP Guidelines.
viii) Study Protocol is not as defined in ICH-GCP Guidelines.
ix) Quantity of drug / trial material to be imported is not described.
v) GMP certificate along with COPP & free sale certificate of the investigational product to be imported are not provided.
vii) Summary of Protocol & Summary of Investigator Brochure are not provided.

3.18.4. Shortcomings were communicated through letter no. F.No.03-104/2019 DD (PS), dated 11th September, 2019, but still response is awaited.

3.18.5. It is pertinent to mention here that as per applicant claim when trial researched & verified from U.S. National Trial Registry it is found that the trial is in early Phase-I stage and they are not recruiting yet, whereas applicant claiming the trial Phase-II studies.

3.18.6. Dr. Jai K. Das, Assistant Professor, Aga Khan University Hospital, Karachi, present before 6th CSC & briefed regarding the trial.

3.18.7. **Decision of 6thCSC Meeting:** -

"The CSC after deliberations deferred the case & decided to get experts opinion, because investigational drug is a chemotherapeutic drug and utilized & tested in the trial for it's off label use.

Applicant will be asked for trial data to be sent to the following experts for their opinion regarding the trail:

i) Maj. Gen. Dr. Salman, Fazaia Medical College, Rawalpindi.
ii) Dr. Yasir, Oncologist, Shifa International Hospital, Islamabad.
iii) Dr. Samiya, ex-Head of Paediatrics Department, PIMS Hospital, Islamabad.

Expert's opinion & recommendations will be presented before CSC in its next meeting."

3.18.8. Experts nominated by the CSC requested for their opinion on the trial through letter number F.No.03-10/2019, dated 27th February 2020, and a reminder also sent to Dr. Samiya & Dr. Yasir on 20th April 2020, but yet response is awaited.

3.18.9. After reevaluation following shortcomings were recorded & communicated to applicant vide letter number F.No.03-10/2019, dated 27th February 2020, but response is yet awaited:

i. Original verified challan for deposited slip number 0801287 is not provided.

ii. As per your submitted reply, if GCSF (Filgen) is an equivalent & similar product, so provide its BA/BE / Bio similarity studies & details regarding other IMPs used in the study at all trial sites.

iii. Investigators Brochure is attached for Neupogen®, whereas Filgen or use of alternate brands of "**Filgrastim**" is not described in the brochure.

3.18.10. **Maj. General Salman Ali** HI (M) (R), Principal & Professor of pediatrics, Fazaia Medical College, Air University, Islamabad, dated 12th April 2020, informed that, he had received & gone through the details of the trial and had opinion that the DRAP may allow the subject trial to be carried out under the international protocol & the stipulated terms & conditions.

3.18.11. Expert opinion from following experts is yet awaited:

i. **Dr. Samiya, ex-Head of Pediatrics Department, PIMS Hospital, Islamabad.**
ii. **Dr. Yasir, Oncologist, Shifa International Hospital, Islamabad.**

3.18.12. Reminder also forwarded to above mentioned experts for their opinion vide letter number F.No.03-10/2019, dated 20th April 2020.

3.18.13. **Dr. Yasir, Oncologist, Shifa International Hospital, Islamabad**, dated 19th May 2020, received on 20th May 2020, informed that, he had received & gone through the details of the trial and had opinion that GCSF can be safely used in such patients without compromising recovery/ outcome.

3.18.14. Submitted for perusal discussion and decision of CSC.

3.18.15. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to defer the case and also decided that as Dr. Samiya, ex-Head of Pediatrics Department, PIMS Hospital, Islamabad didn't replied & not submitted her opinion, so CSC replaced her with Prof. Dr. Munir Malik, Shifa Tameer-e-Millat University, Shifa International Hospital, Islamabad, to get expert opinion on the subject clinical studies.

ITEM IV: MISCELLANEOUS AGENDA ITEMS

4.1) SUB-COMMITTEE ON NATIONAL DATA SAFETY MONITORING (NDSM).

4.1.1. A meeting was conducted in the office of CEO-DRAP 12:30 P.M. on 15th May 2020. CEO-DRAP, Director (PS), Additional Director (PS), Director Admin & DD-CEO were present in the meeting. Director (PS) briefed that upon direction of CEO-DRAP, National Drug Safety Monitoring Board was constituted & fourteen member were nominated. First meeting of the Board/Committee held on 23 April 2020 through Zoom video link in committee room of DRAP. In the meeting it was decided to nominate Prof. Ejaz A. Vohra, Member/General Physician & Mr Shaoukat Ali Javaid Member / Chief Editor Pulse |News to monitor the Clinical trial of Tahir Shamsi on Convalescent Plasma at NIBD Karachi. Additional Director (PS) added that the members of the Board/committee should be from all provinces of Pakistan, Director Admin was of the opinion that if members nominated from all over Pakistan then expenditure of air ticket & other travelling charges will increases.

4.1.2. After discussion it is decided that under the Bio-Study Rules 2017, a sub-committee constituted under the Clinical Study Committee and CEO-DRAP directed that this committee may approved from CSC and if required CSC may increase members.

4.1.3. The following Sub-Committee on National Data Safety Monitoring (NDSM) is being proposed to be approved through Clinical Study Committee:

i. Prof. Aziz Ur Rehman, MBBS, FCPS — **Chairman**
Professor of Medicine.

ii. Dr. Abdur Rashid, Ph.D. Pharmacy, — **Secretary**
Director, Drug Regulatory Authority of Pakistan.

iii. Prof. Abdul Basit,MBBS,FRCP — **Member**
Baqai Medical University, Karachi.

iv. Dr. M. Zeeshan Danish, B.Pharm, MBA, M.Phil.PhD (UK) — **Member**
Post Doc. (CardifI, UK), Fellowship (USA), Ex.Pharmaceutical Expert drug Couns Lahore, Associate Professor Pharmacy. Universiry ofthe Punjab Lahore.

v. Dr.Salman Shahid, Additionat secretary Technical, — **Member**
Specialized Healthcare and Medical Education Department. Govt of Punjab. Lahore.

vi. Dr.M.Suhail, Additional secretary technical, **Member**
Primary and Secondary Healthcare Depanment, Gow of Punjab, Lahore.

vii. Prof.Ejaz A. Vohrta, MBBS,MD (Medicine).FRCP (Medicine) **Member**
Ceneral Physician.

viii. Prof. Iqbal Choudhar1, Director. ICCBS. **Member**
University of Karachi.

ix. Dr. Sumera Rehman, **Member**
Rector, Superior Universiry

x. Dr. Asma Kazi, MBBS FCPS **Member**
Associate Professor of Medicine,
Rashid Latif Medical & Dental College, Lahore.

xi. Dr.Anjum Razzaq ,MBBS,DTCD,MCPS,MPH **Member**
HOD Epidemiology, Institute of Public Health, Lahore.

xii. Mr.Faisal Mushtaq, MSc (Biostat), M.Phil Public Health **Member**

xiii. Mr.Muhammad Umer Farooq, MSC (Biostat). **Member**
M.Phil. Public Health, Demonstrator Biostatistics.

xiv. Mr.Shaukat Ali Jawaid, Chief Editor Pulse News **Member**

4.1.4. Following will be the Terms of Reference (TORs) of Sub-committee on National Drug Safety
Monitoring Committee:

I. Periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy.

II. Make recommendations to Clinical Study Committee concerning the continuation, modification, or termination of the trial. The committee considers study-specific data as well as relevant background knowledge about the disease, test agent, or patient population under study.

III. Prior to initiating any data review, the Sub-Committee on National Data Safety Monitoring (NDSM) is responsible for defining its deliberative processes, including: event triggers that would call for a "scheduled review, stopping procedures that are consistent with the protocol, unmasking (un-blinding), and voting procedures.

IV. The Sub-Committee on National Data Safety Monitoring (NDSM) should review each protocol for any major concern prior to implementation. During the trial, the Sub-Committee on National Data Safety Monitoring (NDSM) should review cumulative study data to evaluate safety, study conduct, and scientific validity and integrity of the trial. The NDSMC should also assess the performance of overall study operations and any other relevant issues, as necessary.

V. The Sub-Committee on National Data Safety Monitoring (NDSM) should conclude each review with their recommendations to Clinical Study Committee as to whether the study

should continue without change, be modified or be terminated. Recommendations regarding modification of the design and conduct ofthe study could include:

a. Modifications of the study protocol based upon the review of the safety data;
b. Suspension or early termination of the study or of one or more study arms because of serious concerns about subjects' safety, inadequate performance, or rate of enrollment;
c. Suspension or early termination of the study or of one or more study arms because study objectives have been obtained according to pre-established statistical guidelines;
d. Optional approaches for Clinical Study Committee and investigators to consider when the Sub-Committee on National Data Safety Monitoring (NDSM) determines that the incidence of primary study outcomes is substantially less than expected.

4.1.5. Submitted for perusal discussion and decision of CSC.

4.1.6. Chairman CSC briefed background of the constitution of the committee and its 1st meeting which was held on 23rd April 2020 via Zoom and also informed that CEO-DRAP directed for its approval from CSC, which is competent forum to constitute sub-committee.

4.1.6. ***Decision of 11th CSC meeting:***

The CSC after detailed deliberation decided to approve following sub-committee on National Data Safety Monitoring (NDSM.)

i. *Prof. Aziz Ur Rehman, MBBS, FCPS* ***Chairman***
Professor of Medicine.

ii. *Dr. Abdur Rashid, Ph.D. Pharmacy,* ***Secretary***
Director, Drug Regulatory Authority of Pakistan.

iii. *Prof. Abdul Basit,MBBS,FRCP* ***Member***
Baqai Medical University, Karachi.

iv. *Dr. M. Zeeshan Danish, B.Pharm, MBA, M.Phil.PhD (UK)* ***Member***
Post Doc. (CardifI, UK), Fellowship (USA), Ex.Pharmaceutical Expert drug Couns Lahore, Associate Professor Pharmacy. Universiry ofthe Punjab Lahore.

v. *Dr.Salman Shahid, Additionat secretary Technical,* ***Member***
Specialized Healthcare and Medical Education Department. Govt of Punjab. Lahore.

vi. *Dr.M.Suhail, Additional secretary technical,* ***Member***
Primary and Secondary Healthcare Depanment, Govt of Punjab, Lahore.

vii. *Prof.Ejaz A. Vohrta, MBBS,MD (Medicine).FRCP (Medicine)* ***Member***
Ceneral Physician.

viii. *Prof. Iqbal Choudhar1, Director. ICCBS.* ***Member***

University of Karachi.

ix.	*Dr. Sumera Rehman,* *Rector, Superior Universiry*	***Member***
x.	*Dr. Asma Kazi, MBBS FCPS* *Associate Professor of Medicine,* *Rashid Latif Medical & Dental College, Lahore.*	***Member***
xi.	*Dr.Anjum Razzaq ,MBBS,DTCD,MCPS,MPH* *HOD Epidemiology, Institute of Public Health, Lahore.*	***Member***
xii.	*Mr.Faisal Mushtaq, MSc (Biostat), M.Phil Public Health*	***Member***
xiii.	*Mr.Muhammad Umer Farooq, MSC (Biostat).* *M.Phil. Public Health, Demonstralor Biostatistics.*	***Member***
xiv.	*Mr.Shaukat Ali Jawaid, Chief Editor Pulse News*	***Member***

Dr. Aamir Jaffrey suggested that the name of Dr. Amjad Mehboob, FCPS, Assistant Professor, infectious diseases, Gajju Khan Medical College, Swabi & it is also decided that Additional Secretaries (Technical) or equivalent from Baluchistan, Khyber Pakhtunkhwa, AJK, & Gilgit Baltistan will be nominated for Sub-Committee on National Data Safety Monitoring (NDSM).

TORs of Sub-Committee on National Data Safety Monitoring (NDSM) will also be shared with National Bioethics Committee for further finalization/delibrations .

4.2) <u>TENURE OF CO-OPTED MEMBERS IN CLSTUDIES COMMITTEE</u>, <u>DECISION BY THE AUTHORITY.</u>

4.2.1. **Bio-Study Rules, 2017** were notified with the approval of Federal Government in exercise of powers conferred by section 23 of drug regulatory Authority of Pakistan Act, 2012 vide **S.R.O.697(I)/2018.**

4.2.2. Hon'able Supreme Court of Pakistan passed orders on 15th of January, 2019, while deciding a case in constitutional petition No. 73/2018 regarding mechanism to commercialize research breakthrough in Pakistan

I. "Clause 7 regarding the constitution of Clinical Studies Committee under the Rule 13 of the Bio-Study Rule, 2017, <u>should be amended to to include following as well</u>"

a. Vice Chancellor, University of Health Sciences or their nominee.
b. Vice Chancellor, University of the Punjab or their nominee.
c. Head of CEMB/CAMB Lahore.

II. In 66th meeting of Authority held on 19th June 2019, Division of Pharmacy Services was directed to immediately process the amendments under section 23 of the DRAP Act 2012, for approval from the Federal Government.

4.2.3. Accordingly file was moved to M/o NHSR&C after approval from CEO, DRAP by Deputy Director (Legal Affairs) for wetting of the Law and Justice Division. After discussion of the Secretary with SAPM, following panel of experts was referred to CEO, DRAP for placing before the DRAP Authority for consideration, recommendation and thereafter to resubmit the draft notification to M/o Law & Justice for vetting:-

i. Dr. Naseem Salahuddin, Director Infectious Diseases Indus Hospital, Karachi, Sindh;
ii. Dr. Aamir Jaffary, Sindh Institute of Urology & Transplantation (SIUT), Karachi, Sindh;
iii. Dr. Rizwana Chaudhry, HOD Gynecologist Holy Family Hospital, Rawalpindi, The Punjab; and
iv. Prof: Dr. Mushtaq Ahmed, Professor of Cardiology, Bacha Khan Medical College Mardan, Khyber Pakhtoonkhwa.

4.2.4. The CSC with prior approval of CEO, DRAP coopted above panel of experts referred by M/o NHSR&C. Later on same was discussed in 75th meeting of the Authority held on 30th January 2020:

The Authority noted that:

1. *Under the Bio-Study Rules, 2017 there is no provision of nomination of any member by name, however under rule 13(1)(j) CSC has the power to nominate any person as a co-opted member.*
2. *Previously, the notification of amendments in the Bio-Study Rules, 2017 was approved in the 66th meeting of the Authority in light of the directions of Hon'able Supreme Court in CP No. 73 of 2018.*

Therefore the Authority decided:

1. To recommend the Clinical Studies Committee to include following as co-opted members for a period of ***6 months*** *only under Rule 13(1)(j) of the Bio-Study Rules, 2017 in light of proposal of M/o NHS, R & C.*

i. Dr. Naseem Salahuddin, Director Infectious Diseases Indus Hospital, Karachi, Sindh;

ii. Dr. Aamir Jaffary, Sindh Institute of Urology & Transplantation (SIUT), Karachi, Sindh;
iii. Dr. Rizwana Chaudhry, Gynecologist Holy Family Hospital, Rawalpindi, The Punjab;
iv. Prof: Dr. Mushtaq Ahmed, Professor of Cardiology, Bacha Khan Medical College Mardan, Khyber Pakhtoonkhwa.

2. To request M/o NHS, R & C to process the notification of amendments in the Bio-Study Rules, 2017, as approved by Authority in its 66th meeting to avoid the delay and non-compliance of Court orders.

4.2.5. Submitted for perusal discussion and decision of CSC.

4.2.6. *Decision of 11th CSC meeting:*

The CSC after discussion decided that at the moment Co-opted members should not be changed as there is a pandemic.

Even after completion of the 6 months CSC may again Co-opt for further six month to utilize their experties.

ANNEXURES:

i. Summary of amendments Azithromycin Clinical Trial (**Annex-I)**:

ii. Summary of Changes endTB v3.3 (Evaluating Newly approved Drugs for multidrug-resistant TB) **(Annex-II)**