**MINUTES OF THE 32ND CLINICAL STUDIES COMMITTEE (CSC), HELD ON 12TH OCTOBER 2021.**

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The 32nd Meeting of the Clinical Study Committee (CSC) was held on 12th October 2021 through Zoom under the chairmanship of Dr. Abdur Rashid, Director Pharmacy Services Division / Chairman (CSC). at the Committee Room, Drug Regulatory Authority of Pakistan, 4th Floor, T.F. Complex, Islamabad.

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

| Sr. No. | Name | Designation |
|---|---|---|
| 01 | Dr. Abdur Rashid. | Chairman CSC / Director, Division of Pharmacy Services-DRAP. |
| 02 | Ahmad Din Ansari. | Secretary CSC/ Additional Director, Division of Pharmacy Services-DRAP. |

3. Following members attended the meeting online through Zoom:

| | | |
|---|---|---|
| 01 | Prof. Brig. (R), Muzammil Hassan Najmi. | Professor of Pharmacology, Foundation University, Islamabad. |
| 02 | Prof. Nadeem Irfan Bukhari. | Professor of Bio-Pharmaceutics & Pharmacokinetics, University of Punjab, Lahore. |
| 03 | Dr. Farhana Badar. | Biostatistician & Epidemiologist, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore. |
| 04 | Dr. Faiza Bashir. | Chairman, Pakistan Health Research Council or his nominee, Islamabad. |
| 05 | Dr. Naseem Salahuddin. | Director Infectious Diseases Indus Hospital, Karachi<br>Co-opted Member. |
| 06 | Dr. Aamir Jaffary | Sindh Institute of Urology & Transplantation (SIUT), Karachi<br>Co-opted Member. |

4. Meeting started with the recitation of holy verses of the Quran by Mr. Ahmad Din Ansari. Chairman, CSC welcomed all the members & appreciated their active online participation through Zoom.

5. Chairman CSC briefed the Committee regarding progress of the sub-committee on preparation of TORs & proforma for evaluation & inspection of ventilator trial applications.

6. Chairman CSC after discussion nominated following sub-committee for preparation of TORs & proforma for evaluation & inspection of Alternative Medicine (Herbal/Unani, Ayurvedic, Chinese or other traditional system of treatment) Clinical Trial applications:

i. **Dr. Abdur Rashid,** Director, Division of Pharmacy Services-DRAP (Chairman)
ii. **Prof. Nadeem Irfan Bukhari**, Member CSC & Professor of Bio-Pharmaceutics & Pharmacokinetics, University of Punjab, Lahore. (Member)
iii. **Dr. Anwar Ahmed Gillani**, Vice Chancellor /Chairman Pakistan Council for Science & Technology, Islamabad. (Member)
iv. **Dr Saiqa Ishtiaq,** Associate Professor, Pharmacognosy**,** University of Punjab, Lahore(Member).
v. **Prof. Dr. Raza Shah,** General Manager, CBSCR-ICCBS, University of Karachi, Karachi. (Member)
vi. **Three Hakeems,** to be nominated/co-opted by Chairman CSC.

**AGENDA ITEM I:**

**CONFIRMATION OF THE MINUTES OF THE 31ST CLINICAL STUDIES COMMITTEE MEETING.**

1. Confirmation of Minutes of 31st CSC meeting held on 26th August 2021. Since, the occurrence of Covid-19 pandemic majority of the meeting are being conducted online through zoom.
2. The minutes of the 31st CSC meeting were shared with all CSC members through email on 3rd September 2021. None of the comments/queries received from the members. Accordingly, decision of the meeting communicated. Minutes are placed again for confirmation to satisfy legal provision.

**Submitted for confirmation of CSC.**

**Decision:**

*All the Members of the CSC unanimously confirmed the Minutes of 31st CSC meeting held on 26th August 2021.*

**AGENDA ITEM II:**

**APPLICATION FOR LICENSE TO ACT AS CLINICAL TRIAL SITE FROM MEDICARE HOSPITAL, RAWALPINDI F. No.15-39/2021 DD (PS).**

The case is an application from Prof. Rizwana Chaudhri, Principal Scientist Global Institute of Human development, Shifa Tameer-e-Millat University (GIHD-STMU), Chief Executive Officer (CEO), Medicare Hospital Rawalpindi, CNIC 37405-8047436-0 of M/s Medicare Hospital, Saidpur Road, Block-F New Katrian Satellite Town, Rawalpindi wherein she has applied to act as Clinical trial Site for phase II, III & IV clinical trials. The application is on Form-I of the Bio-Study Rules 2017 with fee of Rs.100,000/-.

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

| S. No. | Required Documents / Information | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-I of The Bio-Study Rules 2017. | Attached |
| 2 | Prescribed processing fee | Fee challan of Rs.100,000/- attached submitted vide slip No. 8968516887 dated 29-06-2021. |
| 3 | Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors). | Not provided. Only letter from Punjab healthcare commission dated 02-07-2021 is attached mentioning that inspection of premises has been conducted. |

| | | |
|---|---|---|
| 4 | Details of premises including layout plan of the site. | Details of premises not provided, however, layout plan of low ground floor attached where clinical trial site has been highlighted. |
| 5 | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | Not attached, however, list of Sunny Trust International fixed assets has been provided. |
| 6 | Names and qualifications of the above sections along with their staff. | Following is the list of Clinical trial staff.<br>Prof. Dr. Rizwana Chaudhri,<br>Dr. Muttiullah Mutti, Clinical research coordinator,<br>Dr. Asia Kayani, sub-investigator,<br>Dr. Kiran, sub0investigator,<br>Dr. Waqas, MO<br>Miss Mamoona (Staff Nurse)<br>Mr. Masharaf (Staff Nurse) |
| 7 | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | Only name of the services at Medicare Hospital has been provided. |
| 8 | Undertaking on stamp paper | Attached. |

3. After evaluation, following shortcomings has been observed.

i. Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).

ii. Details of premises including layout plan of the site.

iii. Details of the section wise equipment and machinery required for the analytical or bio-analytical (particularly for phase II trials) and clinical studies.

iv. Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.

4. Further, it is submitted that Dr. Rizwana Chaudhri is working as Principal Scientist Global Institute of Human development, Shifa Tameer-e-Millat University (GIHD-STMU), Chief Executive Officer (CEO), Medicare Hospital Rawalpindi, also principal investigator, Co-Chairman Medicare Research Ethics Committee and full-time member of CSC as Co-opted.

5. The reply of the applicant in response to this office letter dated 16th August 2021. Details are following;

| Documents Requested | Reply of applicant |
|---|---|
| Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors). | required in this clause, I would like to bring it in your knowledge that "Medicare Hospital" is a single owner Proprietorship (Sole Proprietorship) hospital under the name of "Prof. Dr. Rizwana Chaudhri" only as per your demand I am submitting you the Official & Residential addresses, Official Address: Medicare Hospital, F-759, Saidpur Road, Siddique Chowk Rawalpindi. Registered & Approved by "Punjab Health Care Commission". Under Registration No. "R20793" in category II-B An inspection team from Punjab Health Care Commission visited Medicare Hospital for detailed inspection and approved the license of Medicare Hospital dated on 02- 07-2021, moreover, letter of 100% completion of PHCC indicators by Medicare Hospital is |

| | |
|---|---|
| | already submitted to PHCC for issuance of License. A copy of Inspection scoring and letter from PHCC is attached for your better understanding. |
| Details of premises including layout plan of the site. | In my previous submission to DRAP dated July 26, 2021, I have submitted the Hospital Premises lay out plan Hereby, I am submitting it again and the Clinical Trial Site Area is highlighted in the layout. Please refer to the attached highlighted layout with this letter Medicare Hospital floor wise details are as follows Please see map we have described our building usage plan with RED PEN also. Total Number of Floors are 07 including 2 basements plus 5 floors. Lower Ground Floor: Two OPD Rooms Highlighted on the map submitted is the clinical trial area. 1st Floor: Project Room Highlighted on the map submitted is the clinical trial area. |
| Details of the section wise equipment and machinery required for the analytical or bio-analytical (particularly for phase II trials) and clinical studies. | As per our previous submission we have already submitted the equipment and machinery list in above regards but we are submitting again an updated list of equipment and machinery attached with this letter. As we are not conducting phase Il trial so please accept our letter for phase III & phase IV Trial only |
| Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | This trial center is a hospital dealing with emergency. Therefore, emergency handling can be done at premises. Emergency handling SOP of Medicare Hospital is already shared with DRAP on our previous submission dated July 26, 2021. We have round the clock coverage of all separate departments with experienced Medical Officers and offering following 24/7 services at premises: Laboratory. Ultrasound Echocardiography. Operation Theater. Pharmacy. Emergency, Ambulance Services. Please note that the there is an MOU for Ambulance services between Medicare Hospital and Abrar Diagnostic Center and a copy of MOU is attached hereby |
| The applicant is working as Principal Scientist Global Institute of Human development, Shifa Tameer-e-Millat University (GIHD-STMU), Chief Executive Officer (CEO), Medicare Hospital Rawalpindi, also principal investigator, Co-Chairman Medicare Research Ethics Committee and full-time member of CSC as Co-opted member. It seems that applicant has conflict of interest | l am associated with GIHD-STMU for research purpose. I am the owner of Medicare Hospital where I do my priority practice and want this facility to be recognized as Clinical Trial Site. Being a member of CSC I would not participate in this study related activity. Moreover, in response to the query generated by the DRAP new emergency IRB committee was formed and office circular is attached which is effective from August 28, 2021. Hereby, I am no more acting as the Co-Chairperson of the IRB committee of Medicare Hospital |

6. Following panel has been constituted by Chairman CSC for inspection of M/s Medicare Hospital, Saidpur Road, Block-F New Katrian Satellite Town, Rawalpindi.

i. Dr. Abdur Rashid, Chairman CSC/ Director, Pharmacy Services Division, DRAP, Islamabad.
ii. Prof. Brig. (R), Muzammil Hassan Najmi, Member Clinical Studies Committee, Professor of Pharmacology, Foundation University, Islamabad.
iii. Dr. Faiza Bashir, Member Clinical Studies Committee, National Bioethics Committee, Islamabad.
iv. Dr. Uzma Malik, Expert/Clinician, Meu Hospital Lahore.
v. Muhammad Ansar, Assistant Director, Pharmacy Services.

7. Due to non-availability of Prof. Brig. (R), Muzammil Hassan Najmi and Dr. Uzma Malik the following panel inspected the premises on **02-09-2021.**

i. Dr. Abdur Rashid, Chairman CSC/ Director, Pharmacy Services Division, DRAP, Islamabad.
ii. Dr. Faiza Bashir, Member Clinical Studies Committee, National Bioethics Committee, Islamabad.
iii. Muhammad Ansar, Assistant Director, Pharmacy Services.

8. The panel submitted the inspection report dully signed by the expert members of inspection team and has recommended the of M/s Medicare Hospital, Saidpur Road, Block-F New Katrian Satellite Town, Rawalpindi to act as Clinical Trial Site for phase III & IV. The recommendation of panel is as under: -

*"The panel inspected the premises of* M/s Medicare Hospital, Saidpur Road, Block-F New Katrian Satellite Town, Rawalpindi *based on infrastructure, pathological services, IT, Archive rooms, emergency and ambulatory services, human resource technical persons, recommends the site for the approval of Phase III & IV only."*

9. **Submitted for the consideration of CSC, Please.**

**Decision:**

*The CSC in pursuance to the recommendations of the inspection panel & in the light of discussion/deliberations unanimously decided to grant licence to M/s Medicare Hospital, Saidpur Road, Block-F New Katrian Satellite Town, Rawalpindi to act as Clinical Trial Site for Phase III & IV Clinical Trials only.*

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**AGENDA ITEM III:**

**APPLICATION FOR LICENSE TO ACT AS CLINICAL TRIAL SITE FROM THE DIABETES CENTRE, ISLAMABAD F. No.15-38/2021 DD (PS).**

The case is an application from Mr. Tahir Mehmood Abbasi CNIC 61101-7475259-7 of M/s The Diabetes Centre, Phulgram Stop, Near Toll Plaza, Murree Expressway, PO Box 635, Barakahu, Islamabad wherein he has applied to act as Clinical trial Site for phase III & IV clinical trials. The application is on Form-I of the Bio-Study Rules 2017 with fee of Rs.100,000/-.

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

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

| | | |
|---|---|---|
| 2 | Prescribed processing fee | Fee challan of Rs.100,000/- attached submitted vide slip No. 22371057707 dated 06-07-2021. |
| 3 | Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors). | Attached. |
| 4 | Details of premises including layout plan of the site. | Attached. |
| 5 | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | Attached. |
| 6 | Names and qualifications of the above sections along with their staff. | Attached. |
| 7 | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | Attached. |
| 8 | Undertaking on stamp paper | Attached. |

3. After evaluation, it has been observed that applicant has attached all necessary documents as per Form-I of the Bio-Study Rules 2017. Further, the fitness of the site to carry out phase III & IV trial may be verified by the panel by inspection.

4. Following panel has been constituted by Chairman CSC for inspection of M/s The Diabetes Centre, Phulgram Stop, Near Toll Plaza, Murree Expressway, PO Box 635, Barakahu, Islamabad.

vi. Brig (Retd) Muzammil Hassan Najmi,
vii. Prof. (Retd) Dr Rizwana Chaudhary.
viii. Dr Abdur Rashid, Director Pharmacy Services, DRAP, Islamabad.
ix. Muhammad Ansar, Assistant Director, Pharmacy Services.

5. Due to non-availability of Prof. (Retd) Dr Rizwana Chaudhary , the following panel inspected the premises on **02-09-2021.**

i. Brig (Retd) Muzammil Hassan Najmi,
ii. Dr Abdur Rashid, Director Pharmacy Services, DRAP, Islamabad.
iii. Muhammad Ansar, Assistant Director, Pharmacy Services.

6. The panel submitted the inspection report dully signed by the expert members of inspection team and has recommended the M/s The Diabetes Centre, Phulgram Stop, Near Toll Plaza, Murree Expressway, PO Box 635, Barakahu, Islamabad to act as Clinical Trial Site for phase III & IV. The recommendation of panel is as under: -

*"The panel inspected the premises of M/s The Diabetes Centre, Phulgram Stop, Near Toll Plaza, Murree Expressway, PO Box 635, Barakahu, Islamabad based on infrastructure, pathological services, IT, Archive rooms, emergency and ambulatory services, the hospital have trained human resource along with foreign experience, recommends for the approval of Phase III & IV."*

7. **Submitted for the consideration of CSC, Please.**

**Decision:**

*The CSC in pursuance to the recommendations of the inspection panel & in the light of discussion/deliberations unanimously decided to grant licence to M/s The Diabetes Centre, Phulgram Stop, Near Toll Plaza, Murree Expressway, PO Box 635, Barakahu, Islamabad to act as Clinical Trial Site for Phase III & IV Clinical Trials only.*

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**AGENDA ITEM IV:**

**APPLICATION FOR LICENSE TO ACT AS BA/BE STUDIES LAB, AT M/S PAKISTAN DRUG TESTING AND RESEARCH CENTER, LAHORE F. No.03-02/2015 ADC (PS).**

The case is an application from Prof. Dr. Zaka-Ur-Rehman, COO, PDTRC, wherein he has stated that this is in reference to DRAP letter No. F.3-2/2015-ADC (PS) Dated 9th July, 2015 wherein license/approval for the conduction of BA/BE studies was granted for a period of 2 years effective from 9th July, 2015. BA BE studies was not performed because BE Center was not functional because of administrative/ management/financial issues during the period from 2015 to 2020. Punjab Industrial Estates Development & Management Company (PIEDMC), Ministry of Industries, Commerce, Investment and Skill Development, Govt. of the Punjab, took a bold initiative in April 2020 and has provided requisite budget/infrastructure/ HR with the mission to sustain the status of PDTRC as WHO Pre-Qualified and ISO Certified Lab. Alhamdulillah! With the grace of Almighty Allah and with sincere efforts of BOD-PIEDMC/ BOM-PDTRC Staff, now PDTRC is operational and heading towards excellence in the field of Drag Microbiological testing, Stability studies & conduction of BA/BE studies at PDTRC. Recently, DRAP has granted license to PDTRC to act as Bioanalytical Laboratory vide License No. BAL-001 (Form-V) Dated 19th October, 2020 in compliance to GCP & GLP guidelines. The license/approval No. F.3-2/2015-ADC (PS) from DRAP for conduction of BA/BE studies at PDTRC was expired on 8th July, 2017 and the renewal was not requested. The requisite infrastructure and experienced BE regular/ visiting staff is available at PDTRC for conduction of BE studies at Bioequivalence Center, PDTRC in compliance to international BE regulatory standard (WHOFDA/DRAPICH) guidelines.

2. The application is on prescribed Form-I of the Bio-Study Rules 2017 along with fee of Rs.300000/- deposited vide challan no.2013495, dated 10th March 2021.

3. The application evaluated according pre- requisites as mentioned in Form-I of the Bio-Study Rules 2017, and status of application is as follows:

| S. No. | Required Documents / Information | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-I of The Bio-Study Rules 2017. | Attached but without signature and seal of the firm/ company |
| 2 | Fee | Not endorsed from B&A Division of DRAP |
| 3 | Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors). | Not Attached |
| 4 | Details of premises including layout plan of the site. | Not Attached |

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

4. After evaluation following shortcoming observed and communicated to applicant:
   i) Application on prescribed Form-I of The Bio-Study Rules 2017 dually signed by the applicant along with seal of the Firm/ Company.
   ii) Fee Challan Endorsed by Budgets and Accounts division of DRAP.
   iii) 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).
   iv) Details of premises including layout plan of the site.
   v) Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.
   vi) Names and qualifications of the above sections along with their staff.
   vii) Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.
   viii) Undertaking on stamp paper.

5. Following is reply from Dr. Zaka-Ur-Rehman, Chief Operating Officer, PDTRC, Lahore in response to this office letter F.No.03-02/2015 dated 13th April, 2021. The submitted reply is evaluated according to pre- requisites as mentioned in Form-I of the Bio-Study Rules 2017, and status of application is as follows:

| **S. No.** | **Required Documents / Information** | **Remarks** |
|---|---|---|
| 1 | Application on prescribed Form-I of The Bio-Study Rules 2017. | Attached |
| 2 | Fee | Submitted vide challan No. 2013495 dated 10.03.2021 and Slip No. 9736944402 dated 6th August 2021. |
| 3 | Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors). | Attached |
| 4 | Details of premises including layout plan of the site. | Layout plan attached. |
| 5 | Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies. | Attached |
| 6 | Names and qualifications of the above sections along with their staff. | Attached. |

| | | |
|---|---|---|
| 7 | Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. | BOMSIE will provide ambulance facility for Bio-equivalence BE study period.<br>MOU for emergency health cover has been signed b/w PDTRC & UOL Teaching Hospital. |
| 8 | Undertaking on stamp paper | Attached. |

6. Following panel was constituted by Chairman CSC for inspection of Pakistan Drug Testing and Research Centre, Lahore. The panel Prof Dr Javed Akram, V.C, UHS, Lahore.

i. Prof Dr Javed Akram, VC, UHS, Lahore.
ii. Prof Dr Nadeem Irfan Bukhari, Dean College of Pharmacy, University of Punjab, Lahore.
iii. Dr Farhana Badar, Biostatistician, SKCMH&RC, Lahore.
iv. Dr Abdur Rashid, Director Pharmacy Services, DRAP, Islamabad.
v. Rana Ahsan Ul Haq Athar, Assistant Director, Pharmacy Services.

7. The following panel inspected the premises of M/s PTDRC on **27-08-2021.**

i. Prof Dr Nadeem Irfan Bukhari, Dean College of Pharmacy, University of Punjab, Lahore.
ii. Dr Sualeha Riffat Bukhari, Co-opted member.
iii. Dr Farhana Badar, Biostatistician SKCMH&RC, Lahore.
iv. Dr Abdur Rashid, Director Pharmacy Services, DRAP, Islamabad.
v. Prof Dr Nadeem Afzal. UHS.

8. Due to non-availability of *Prof Dr Javed* Akram, Prof Dr Nadeem Afzal UHS Lahore has joined the Inspection.

9. The panel submitted the inspection report dully signed by the expert members of inspection team and has recommended the PDTRC, Lahore as BA/BE Centre. The recommendation of panel is as under: -

"*Keeping in view of infrastructure, equipment available in the laboratory, SOPs, Record documents, human resource and their experience, already experienced in bio-equivalence, accreditation by WHO, 17025 certifications, the panel unanimously recommends BA/BE Centre of Pakistan Drug Testing and Research Centre, Commercial area, North Sundar Industrial area, Lahore. However, Bio-analytical license will remain separate.*
*Prof Dr Javed Akram did not joined the panel, Prof Javed Akram said that Prof Dr Nadeem Afzal UHS Lahore will join, who is also one inspector."*

10. **Submitted for the consideration of CSC, Please.**

**Decision:**

*The CSC in pursuance to the recommendations of the inspection panel & in the light of discussion/deliberations unanimously decided to grant licence to M/s Pakistan Drug Testing and*

*Research Centre, Commercial area, North Sundar Industrial area, Lahore to act as BA/BE Studies Center.*

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**AGENDA ITEM V:**

**APPLICATION FOR APPROVAL OF USE OF COMMERCIAL VACCINE IN CLINICAL TRIAL TITLED "A GLOBAL MULTICENTER, RANZOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED, ADAPTIVE DESIGNED PHASE III TRIAL TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF RECOMBINANT NOVEL CORONA VIRUS VACCINE (ADENOVIRUS TYPE 5 VECTOR) IN ADULTS 18 YEARS OF AGE AND OLDER" F. No.03-69/2021-DD (PS).**

Application is from Dr. Ghazala Parween, Chief BPD, National Institute of Health, Islamabad, wherein they have requested for approval of use of commercial vaccine in Clinical Trial.

2. It is submitted that, the subject trial application for booster dose was discussed in the 27th CSC meeting held on 24th June 2021 & the CSC decided as follows:

The CSC after detailed deliberation and discussion decided to approve the protocol amendments (CS-CTP-AD5NCOV-III Version 2.0) in clinical trial titled, "A Global Multicenter, Randomized, Double Blind, Placebo Controlled, Adaptive Designed Phase III Trial to Evaluate the Efficacy, Safety and Immunogenicity of Recombinant Novel Corona Virus Vaccine (Adenovirus Type 5 Vector) in Adults 18 Years of Age and Older". The trial as per amended protocol will be conducted at the following Clinical Trial Sites in the light of their respective IRB approvals:

i. *Aga Khan University Hospital, Karachi.*
ii. *The Indus Hospital, Karachi.*
iii. *Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.*
iv. *Shifa International Hospital, Islamabad.*
v. *University of Health Sciences, Lahore.*

3. CSC also approved 16,560 doses of investigational product to be used in this trial.

4. Accordingly, decision of CSC was communicated to applicant vide letter number F.No.16-27/2021, dated 24th June 2021.

5. Now applicant forwarded application for approval of use of commercially available vaccine in the trial as the export licence of the manufacturer (i.e. M/s CanSino Biologicals, China) has been expired & it takes time for renewal.

6. Further applicant informed that, 8400 out of 16560 doses were shipped remaining doses (i.e.8160) need to be procured on commercial ground to complete amended protocol of the study to avoid any delay.

7. It is submitted that, as per the Bio-Study Rules it is an amendment in approved protocol & regarding amendment Rule 8(10) & (11) speaks as under: -

> *"(10) No amendments in the approved protocol of trial or study can be made without seeking prior approval from CSC.*

*(11) Any amendment or report to the investigational study, shall not contain any intrigue statement of material fact or omit material information required by this part as Pakistan GCP or ICH GCP guidelines".*

8. Moreover, Rules 12 of Bio-Study Rules regarding use of commercially available product in already approved Clinical Trial is reproduced below: -

*"(12) The investigational product shall not be promoted or distributed for commercial purposes and quantities should be justified by the requirement of investigational study or clinical trials."*

9. ICH-GCP guidelines adopted by DRAP for Investigational Medicinal Products (IMPs) defines as following: -

***"4.6 Investigational Product(s)***
***4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.***

***5.14 Supplying and Handling Investigational Product(s)***
*5.14.1* ***The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).***
*5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g., approval/favourable opinion from IRB/IEC and regulatory authority(ies)).*
*5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).*
***5.14.4 The sponsor should:***
***(a) Ensure timely delivery of investigational product(s) to the investigator(s).***
*(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).*
*(c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g., for deficient product recall, reclaim after trial completion, expired product reclaim).*
*(d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition."*

10. In view of above submission as per Rules and ICH guidelines adopted by DRAP, it is proposed that: -

a) The applicant has intimated about the expiry of export license and its renewal, so he should ask the sponsor for renewal of the export license as it is their responsibility to ensure the timely delivery of the required investigational medicinal product (IMP) for trial as this is not the mandate of DRAP.
b) As it is a multi-country trial and hopefully none of the trial site globally will be using product other than the IMP provided by the sponsor. If so the applicant may apprise regarding this.
c) The applicant should get permission/clearance in writing from sponsor with justification for use of this vaccine with EUA status as IMP and its utilization globally as it is multi-country trial.

11. The matter was sent to CEO, DRAP for information as it was desired in the applicant's request, the direction is as under: -

"It is submitted that matter be resolved at competent forum i.e. Clinical Study Committee".

12. In light of above, the case is submitted for the consideration of CSC, Please.

13. The secretary CSC appraised the Committee regarding provisions laid down in Bio-Study Rules & ICH-GCP guidelines for the procurement/supply of *Investigational Medicinal Product (IMPs)*as mentioned in preceding paras 7-9 above and that the applicant should approach the sponsor for renewal of export license for *Investigational Medicinal Product (IMPs)*as it is their responsibility for timely & uninterrupted supply/delivery of required *Investigational Medicinal Product (IMPs)*for trial. It is neither the mandate of DRAP nor CSC. The Committee was also briefed that the applicant has not even disclosed whether EUA status vaccine being used as IMP at any other site or otherwise.

***Decision:***

*CSC after deliberation / detailed discussion decided to defer the case as uninterrupted & timely supply of the Investigational Medicinal Product (IMPs) is responsibility of the trial sponsor.*

*It is neither the mandate of DRAP nor CSC. The Committee also directed the applicant to submit the updated progress report of the study for its review/appraisal.*

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**AGENDA ITEM VI:**

**TERMS OF REFERENCE & PROFORMA FOR EVALUATION & INSPECTION OF CLINICAL VALIDATION OF VENTILATOR TRIAL APPLICATIONS.**

Clinical Studies Committee (CSC) in its 19th meeting held on 12th February 2021 constituted the following sub-committee to develop TORS & proforma for evaluation & inspection of ventilator trial applications.

i. Biomedical engineers
ii. Anesthetist
iii. Pulmonologist
iv. Dr. Faiza Basheer
v. Prof. Dr. Javed Akram
vi. Dr. Abdur Rasheed
vii. Any other expert co-opted by the sub-committee.

2. Accordingly, followings experts were nominated by the Chairman CSC.

i. Muhammad Daniyal Sheikh, Biomedical Engineer, Isolation Hospital and Infection Treatment Center, NIH, Islamabad.
ii. Dr. Zaid, Pulmonologist, Isolation Hospital und Infection Treatment Center, NIH, Islamabad.
iii. Prof. Dr. Iqbal Memon, Anesthetist/ Intensivist, Principal HBS Medical College Hospital, Tramri Chok, Islamabad.
iv. Dr. Murtaza Najabat Ali, CEO, NHT, NUST, Islamabad (coopted expert).

1. The 1st and 2nd Meeting of the Sub-committee was held on 07th September 2021 and 14th September, 2021 under the chairmanship of Dr. Abdur Rashid, Director Pharmacy Services Division in Committee Room-I, 4th Floor, Drug Regulatory Authority of Pakistan, Islamabad.

2. After due deliberation and discussion, the sub-committee framed the three sets of TORS & proforma for evaluation & inspection of clinical validation of ventilator trial applications in following sequence.
3.

i. Terms of reference for evaluation and inspection of ICU ventilators for brain Dead/fully sedated patients **(Annex-I)**
ii. Terms of reference for evaluation and inspection of ICU ventilators for paralyzed/ sedated patients. **(Annex-II)**
iii. Terms of reference for evaluation and inspection of ICU ventilators for non-sedated patients. **(Annex-III)**

**4. Submitted for the consideration of CSC, Please.**

***Decision:***

*CSC after detailed deliberation & discussion decided to approve the following TORs & Proforma for Evaluation & Inspection of Clinical Validation of Ventilator Trial Applications, prepared by the sub-committee on the matter:*

*i. Terms of reference for evaluation and inspection of ICU ventilators for brain Dead/fully sedated patients **(Annex-I)***
*ii. Terms of reference for evaluation and inspection of ICU ventilators for paralyzed/ sedated patients. **(Annex-II)***
*iii. Terms of reference for evaluation and inspection of ICU ventilators for non-sedated patients. **(Annex-III)***

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**AGENDA ITEM - VII:**

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

The case is an application from Mr. Asim Munir, Project Manager, CNIC No 35202-4375948-5 of M/s DRK, Pharma Solution, Lahore wherein the applicant has requested for approval or registration of clinical trial titled "A Global, Multi-center, Randomized, Double-Blind, Placebo-Controlled, Phase III Clinical Study to Evaluate the Efficacy, Safety, and Immunogenicity of Sequential Immunization of Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01) Against COVID-19 in Healthy Adults Aged 18 Years and Older after the Vaccination of 2 Doses of Inactivated Vaccines". The application is on Form-II of the Bio-Study Rules 2017.

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

| S. No. | Document | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-II | Attached |

| | | |
|---|---|---|
| 2 | Prescribed processing fee | Fee of Rs.200,000/- submitted Slip No. 59705338481 dated 02.08.2021. |
| 3 | Investigator Brochure (s) | Attached |
| 4 | Final protocol | Attached. |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached. |
| 6 | List of participating countries | Pakistan, Turkey, Mexico, Malaysia. |
| 7 | Phase of trial. | Phase III |
| 8 | Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material. | Vaccine recombinant SARs COV 2 fusion protein vaccine (V-01)<br>4,800 vials<br>Placebo 4,800 vials<br>Total 9600 vials |
| 9 | Site of the trial | Agha Khan Hospital Karachi<br>Dow University of Health Sciences<br>Central Park Medical College and Hospital, Lahore.<br>Sindh Infectious Diseases Centre, Dow University CTU<br>Shifa International Hospital, Islamabad<br>SKMCH&RC, Lahore,<br>Al Khidmat Foundation,<br>Surayya Azeem Waqaf Hospital, Lahore,<br>Central Hospital Gujranwala. |
| 10 | Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members. | IRB approval SKMCH&RC, Lahore not attached. |
| 11 | Approval of National Bio-ethics Committee (NBC) | Attached.<br>Ref:No.4-87/COVID-79/21/129, Dated 30th July 2021. |
| 12 | CV's of the Investigators | CV of<br>Syed Faisal Mehmood, Associate professor, Principal Investigator.<br>Dr. Shoba Luxmi, Associate Prof. at Dow university of Health Sciences<br>Dr. Muneeba Ahsan, Assistant Professor at Sindh Infectious Diseases Hospital and Research Center, |

| | | |
|---|---|---|
| | | Dr. Mian Amjad Sohail, Director Shifa research Centre,<br>Dr. Salman Athar, Anesthetist, Central Hospital Gujranwala,<br>Dr. Muhammad Ahmad, Central Park Medical college and Hospital,<br>Dr. Muhammad Asif Naveed, Associate Professor, |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | GMP certificate and DML attached of M/s Livzon Mabpharm Inc. is attached in Chinese language and translation by Delsalt Consulting Co. ltd. |
| 14 | Pre-clinical/clinical safety studies | Attached |
| 15 | Summary of Protocol | Attached. |
| 16 | Summary of Investigator Brochure | Attached. |
| 17 | Adverse Event Reporting Form | Attached. |
| 18 | No of patients to be enrolled in each center. | Total 8,000 subjects and 1000 in each site will be recruited. |
| 19 | Name of Monitors & Clinical Research Associate | DRK Pharma Solution, Lahore. Manisha Lohano, Yusra Maryam, Saad Ali Shah, Roha Badar, Fatima Aleem, Bakhtawar Abid, Mohsin Ali, Salman Tariq, Abdullah Mir, Khizar Hayat, Haina Sarwar, Hasnain Hashmi, Ali Faizan, Sana Rafique. |
| 20 | Evidence of registration in country of origin. | Not attached |
| 21 | Copy of registration letter (if registered in Pakistan) | N/A |
| 22 | Sample of label of the investigational product / drug. | Attached. |
| 22 | Duration of trial | 20 months. |
| 23 | Undertaking on stamp paper. | Attached. |

3. The case was discussed in the 31st CSC meeting held on 26th August 2021 & the Committee decided as follows:

Decision:

*The CSC after deliberation / detailed discussion decided to defer the case till fulfilment of all prerequisites of the application as briefed by Secretary CSC & further review of the trail application*

*by expert members of CSC as per international practices & WHO recommendations and in the light of safety data worldwide regarding mix & match vaccine trial/study.*

4. Accordingly, decision of the Committee was communicated on 08th September 2021. In response applicant has provided some documents regarding booster vaccine trial/study, all documents provided by the applicant has been emailed to the experts on dated 08th October, 2021 but still no comments have been received.

5. A letter was also issued on 08th October 2021 for invitation & fulfillment of remaining prerequisites but response is yet awaited.

**6. <u>The case is submitted for consideration of CSC</u>.**

**7.** Dr Syed Faisal Mehmood, Associate professor, Principal Investigator of the trial joined the meeting in-person & briefed the Committee regarding the safety of the trial as apprehended by CSC members during the previous meeting.

He also answered the questions raised by the members. The CSC members were satisfied with the presentation of the case by the PI. Mr. Asim Munir, Project Manager, M/s DRK, Pharma Solution, Lahore also furnished some documentary evidences with respect to mix and match trial studies carried out in different countries.

**<u>Decision:</u>**

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

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**<u>AGENDA ITEM - VIII:</u>**

**<u>ADVERTISEMENT FOR RECRUITMENT OF SUBJECTS FOR CLINICAL TRIAL TITLED "A GLOBAL, MULTI-CENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE III CLINICAL STUDY TO EVALUATE THE EFFICACY, SAFETY, AND IMMUNOGENICITY OF SEQUENTIAL IMMUNIZATION OF RECOMBINANT SARS-COV-2 FUSION PROTEIN VACCINE (V-01) AGAINST COVID-19 IN HEALTHY ADULTS AGED 18 YEARS AND OLDER AFTER THE VACCINATION OF 2 DOSES OF INACTIVATED VACCINES". BY M/S SHIFA INTERNATIONAL HOSPITAL, ISLAMABAD.</u>**

The case is advertisement on the social media regarding the recruitment of trial subjects for Clinical Trial titled, "*Clinical Trial Titled "A Global, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Phase III Clinical Study To Evaluate The Efficacy, Safety, And Immunogenicity Of Sequential Immunization Of Recombinant Sars-Cov-2 Fusion Protein Vaccine (V-01) Against Covid-19 In Healthy Adults Aged 18 Years And Older After The Vaccination Of 2 Doses Of Inactivated Vaccines"* for booster dose (Single dose) of vaccine by Livzon (Fusion Protein Based Vaccine) mentioning to contact below named persons: -

i. Dr Ahmed Sohail 0330-2001432
ii. Mehwish Rafique 0330-2001433
iii. Mohsin Ali 0330-2001434

2. As per record of Drug Regulatory Authority of Pakistan (DRAP) the trial being claimed in the advertisement has not been yet approved by the DRAP and advertisement for subject recruitment prior to the approval of trial is not only illegal but also unethical.

3. In view of above a letter for clarification in this regard was issued by the Division on 16th September, 2021, F.No.03-74/2021 DD(PS).

4. In response to above said communication Dr Mian Amjad Sohail, Director Medical Services, clarified and submitted as under: -

i. This was never made public or with immediate intention of advertisement. It was however circulated only among our core research team for review, suggestion and approval, only. There were no print copies ordered or printed as well.
ii. There was no circulation of hard copies, broachers or display of any material on social and print media even within Shifa premises or websites as we were waiting for formal approval for the trial from DRAP).
iii. Additionally, for DRAP approval we were in the process finalizing and collecting all such awareness material pending final copies for submission to DRAP.
iv. We had received a single call regarding subject recruitment and we had replied the trial has not been approved by DRAP till date. The caller was informed that we will open recruitment once officially approved by DRAP.
v. The trial has been approved by National Bioethics Committee, Pakistan.
vi. This protocol was also approved by Shifa International Hospital, IRB and Ethics Committee.
vii. We humbly submit that we at Shifa are a DRAP approved CTU and always comply and follow all national and international regulations and rules related to trials including regulatory authorities including DRAP.
viii. Our site has always followed all legal and ethical parameters and will Insha'Allah continue to comply and assure that all research requirements/rules/regulations are fulfilled.
ix. We regret for any misunderstanding that this may have created.
x. It is requested to hereby withdraw your letter issued dated 16th September, 2021, F.No.03-74/2021 DD(PS).

**5. <u>The case is submitted for consideration of CSC</u>.**

6. Prof. Dr. Ejaz A. Khan, Consultant Pediatrician & Infectious Disease Specialist, Miss Mehwish Rafique & Dr. Ahmad Sohail, Shifa International Hospital, joined the meeting in-person. Prof. Dr. Ejaz A. Khan, briefed the Committee that, they haven't advertised for recruitment of trial subjects on any type of media. This was never made public or with immediate intention of advertisement. It was however circulated among our core research team for review, suggestion and approval, only. There were no copies ordered or printed as well. Whereas they have developed that advertisement for recruitment, which will be for utilization after formal approval of the trial from DRAP. They also regretted for any misunderstanding and inconvenience due to this development.

**<u>Decision:</u>**

*The CSC after deliberation / detailed discussion decided to drop the case in the light of clarification given by Prof. Dr. Ejaz A. Khan Consultant Pediatrician & Infectious Disease Specialist of M/s Shifa International Hospital, Islamabad.*

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**<u>AGENDA ITEM IX</u>:**

**<u>AMENDMENTS IN ALREADY APPROVED CLINICAL TRIAL TITLED "*TRANSNASAL CAPSULE ENDOMICROSCOPY FOR VISUALIZATION OF THE SMALL INTESTINE IN ENVIRONMENTAL ENTERIC DYSFUNCTION (EED) POPULATION IN PAKISTAN*". F. No.03-18/2020-DD (PS)</u>**

Application submitted by Dr. Sayed Asad Ali, Professor, Department of Pediatrics & Child Health, Associate Dean, Research, Medical College, Aga Khan University, Karachi, wherein application is a request for amendments in already approved protocol Version 1.0 to Version 1.5 of Clinical Trial titled, *"Transnasal Capsule Endomicroscopy for Visualization of the Small Intestine in Environmental Enteric Dysfunction (EED) Population in Pakistan"*.

02. Summary of amendments submitted as follows:

*i. We are amending the study population to include 30 women in their 2nd trimester of their pregnancy to be imaged with the Transnasal Endoscopy Device. All women will be recruited at AKU Karachi and its secondary hospitals in Karachi (Amended protocol, Pregnant women data collection and consent forms have been added)*

*ii. We have made minor changes in the transnasal imaging procedure to allow for maneuvering of the TNIT and have added the option to allow for syringe aspiration through the TNIT tube to improve image quality.*

*iii. Addition of COVID-l9 testing and status documentation for all subjects including children and pregnant women (updated consent forms, screening/enrollment forms documentation).*

*iv. We have updated the device documentation to include the latest versions of the devices and changes in the procedures.*

*v. We have also included the option of remote monitoring and assistance during the procedure by the staff at the Tearney Lab at MGH in lieu of physical presence due to COVID-19 related travel restrictions.*

*vi. We have added blood and fecal samples for children under 5 years (changes reflected in the consent form and Data collection tools).*

*vii. Data collection tools for children 6 months to 59 months have been amended to reflect the coVlD-l9 screening questions, additional screening questions for the imaging procedure, questions on geophagy, some additional and clinical assessment questions have been added and ire highlighted.*

*viii. Lab sample collection form has been added.*

*ix. Experimental adverse event form for capsule procedure has been amended and a new form for the transnasal procedure has been added.*

03. Following supporting documents are attached along with amendment application:

i. Prescribed fee for miscellaneous request paid vide challan number 2084801 dated, 28th April 2021, need to be verified from Budget & Accounts Division-DRAP.
ii. Amended protocol version 1.5 track change copy.
iii. IRB approval letter reference No. Nil, dated 30th January 2021.
iv. NBC approval letter for amendment & extension, reference No. 4-87/NBC-429 Y2 Extension/21/1272 dated 09th February 2021.
v. Trial progress report.
vi. Revised Informed Consent Forms (English, Urdu & Sindhi).
vii. Revised Adverse Event Reporting forms.
viii. Revised Informed Consent Forms for Parental Permission Document (English, Urdu & Sindhi)
ix. Investigator's Brochure Version 1.2 (Trans Nasal Endomicroscopy Instruction for Use).
x. Pregnancy Outcome Forms Version 1.0
xi. Trans Nasal Endomicroscopy Device Description 1.2
xii. Trans Nasal Endomicroscopy Compact Imaging System 1.1 (Instruction for Use)
xiii. Trans Nasal Endomicroscopy Compact Imaging System 1.1 (Description)
xiv. Screening & Recruitment form for Pregnant Women.
xv. Pre-screening & Illness Assessment 24-48 hours before Procedure for Pregnant Women.
xvi. IRB Review Certificate from the Partners Human Research System.

04. After scrutiny of amendment application following shortcomings observed:

i. Application submitted for amendment is not signed in original.
ii. Submitted challan is not verified from Budget & Accounts Division of DRAP.

05. Shortcomings were communicated to the applicant vide letter even number dated 08th March 2021, yet response is awaited. Accordingly, applicant submitted revised application & progress report, signed in original and file forwarded to Division of Budget & accounts for verification of challan.

06. Technical documents were shared with expert CSC members through email on 30th September 2021 for review & comments.

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

08. Dr. Sheraz Ahmad joined the meeting through Zoom as representative of PI & briefed the Committee regarding amendments & answered the questions raised by the CSC members.

**Decision:**

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

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**AGENDA ITEM X:**

**EXTENSION IN TRIAL DURATION & AMENDMENTS IN ALREADY APPROVED CLINICAL TRIAL TITLED "CHLOROQUINE/ HYDROXYCHLOROQUINE PREVENTION OF CORONAVIRUS DISEASE (COVID-19) IN THE HEALTHCARE SETTING; A RANDOMIZED, PLACEBO-CONTROLLED PROPHYLAXIS STUDY (COPCOV)". F. No.03-43/2020-DD (PS)**

Application is from Dr. Muhammad Asim Beg, Professor & Consultant Parasitologist, Aga Khan University, dated 11th June 2021, along with a fee of Rs.25000/- deposited vide Challan No.48751437 dated 09th June 2021. Wherein request has been made for amendments in already approved protocol of clinical trial titled "Chloroquine/ Hydroxychloroquine Prevention of Coronavirus Disease (COVID-l9) in the Healthcare Setting; a Randomized, Placebo-controlled prophylaxis study (COPCOV)".

2. Applicant provided following documents:

i. Application along with prescribed fee.
ii. AKUH-IRB approval for amendment of protocol version from 5.0 to 6.0.
iii. NBC- amendment approval letter reference No.4-87/NBC-COVID-28-Amend/21/, dated 24th May 2021.
iv. Amended protocol version 6.0 along with its summary.
v. Amended Investigator's Brochure version 6.0.
vi. Revised Subjects Screening Form.
vii. Revised Patient Information Sheet.
viii. Revised Informed Consent Form (English & Urdu)
ix. Prescribed fee of Rs.25000/- for trial extension application submitted vide challan number 67145995038, dated 17th October 2021

3. Subject clinical trial (Protocol version 5.0) was approved on 28th August 2020 for a period of 05 months, which was expired on 27th January 2021.

4. Technical documents (Amended protocol version 6.0 track change copy & other) were shared with expert CSC members through email on 30th September 2021 for review & comments.

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

6. Dr. Anum Dr. Momin Qazi & Dilshad Begum joined the meeting through Zoom as representative of PI from Aga Khan University Hospital, Karachi & briefed the Committee regarding amendments & need for extension and answered the questions raised by the CSC members.

7. Prof. Brig. (R), Muzammil Hassan Najmi, Dr. Abdur Rashid, Dr Naseem Salahuddin, Dr. Aamir Jaffary & other CSC members raised questions about the study & informed that in first wave of COVID-19 after many clinical studies it is published that, Chloroquine/ Hydroxychloroquine are not effective against COVID-19 as these molecules have no antiviral effects. It was also observed that there is no such data provided by the PI by which it can be evaluated that there is a need of extension in the trial duration.

**Decision:**

*The CSC after deliberation / detailed discussion decided to defer the application for amendment & extension as no data has been furnished as evidence to substantiate the efficacy of Chloroquine/ Hydroxychloroquine for Prevention/prophylaxis of Coronavirus Disease (COVID-19).*

*Further it is decided that the applicant Dr. Muhammad Asim Beg who is also the PI of the study shall submit trial data for evaluation of IMPs efficacy & he will personally participate & brief the CSC in its next meeting regarding the reasons for amendment & extension of the trial as the studies have become obsolete worldwide.*

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**AGENDA ITEM XI:**
**NOMINATION & APPROVAL OF SRA COUNTRIES LIST FOR INCORPORATION IN REVISED GUIDELINES FOR CONDUCT OF CLINICAL TRIALS IN REFRENCE TO ASSIGNED INSTITUTIONAL DEVELOPMENT PLAN (IDPS) (WHO'S GLOBAL BENCHMARKING TOOLS). F. No.08-16/2021-DD (PS)**

It is submitted that, some of Institutional Development Plan (IDP) as per indicators mentioned in WHO Global Benchmarking Tools were assigned to Division of Pharmacy Services (Clinical Trial Section) vide letter number 4-2/2020-QMS.

2. Accordingly, assigned tasks are reviewed & required amendment/clarification incorporated in the Guidelines for Conduct of Clinical trials. Revised guidelines were placed before CSC in its 27th meeting & the CSC after review approved these guidelines.

4. After approval of CSC, the guidelines were forwarded to QMS-Section for review & subsequent submission to the Authority for approval. In the revised guidelines following list of WHO approved list of Stringent Regulatory Authorities/Countries was included:

| S.No. | SRAs Countries | S.No. | SRAs Countries | S.No. | SRAs Countries |
|---|---|---|---|---|---|
| 01 | Australia | 13 | Greece | 25 | Norway |
| 02 | Austria | 14 | Hungary | 26 | Poland |
| 03 | Belgium | 15 | Iceland | 27 | Portugal |
| 04 | Bulgaria | 16 | Ireland | 28 | Romania |

| | | | | | |
|---|---|---|---|---|---|
| 05 | Canada | 17 | Italy | 29 | Slovakia |
| 06 | Cyprus | 18 | Japan | 30 | Slovenia |
| 07 | Czech Republic | 19 | Latvia | 31 | Spain |
| 08 | Denmark | 20 | Liechtenstein | 32 | Sweden |
| 09 | Estonia | 21 | Lithuania | 33 | Switzerland |
| 10 | Finland | 22 | Luxembourg | 34 | United Kingdom |
| 11 | France | 23 | Malta | 35 | United States of America |
| 12 | Germany | 24 | Netherlands | | |

6. QMS Section reviewed the revised guidelines & proposed some minor amendment which were incorporated in the guidelines & further it was suggested that, CSC may recommend the list of countries to be considered as stringent regulatory authorities for the purpose of reliance.

7. It is proposed that, CSC may nominate & approve some of SRA Countries as per Rule 13 (8), for reliance & consideration of relevant clinical trial decisions, reports or other information. After nomination & approval of the CSC, the approved list will be incorporated in the revised guidelines & will be forwarded to QMS-Section for review & subsequently to the CEO-DRAP for final approval.

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

**Decision:**

*The CSC after deliberation / detailed discussion decided to approve the following Stringent Regulatory Authorities for reliance & consideration of relevant clinical trial decisions, reports or other information as provided under Rule 13 (8) of the Bio-Study Rules & for inclusion in the revised Conduct of Clinical Trial Guidelines.*

i. The United States Food and Drug Administration (U.S. FDA)
ii. The Medicines and Healthcare products Regulatory Agency, UK (MHRA)
iii. The European Medicines Agency (EMA).
iv. Health Canada.
v. The Therapeutic Goods Administration (TGA), Australia.
vi. Pharmaceutical & Medical Devices Agency-PMDA, Japan.

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**AGENDA ITEM XII: APPROVAL OF CLINICAL STUDIES COMMITTEE (CSC) OPERATIONAL MANUAL. F. No.08-20/2021-DD (PS)**

Reference to the Institutional Development Plans (IDPs) assigned after 5th meeting of management review committee (MRC) a letter received on 06th June 2021, forwarded by Additional Director QMS-DRAP, for achievement of WHO-Global Benchmarking Tools level-III.

2. Following IDPs were assigned for preparation of Clinical Studies Committee Operational Manual & maintenance of professional profile:

| Sr. No. | Tasks Assigned as per IDP | Nature of Activity |
|---|---|---|
| 7. | CT02.01: There is a defined structure with clear responsibilities to conduct clinical trial oversight activities | Maintenance of CSC operational manual. |
| 8. | CT03.01: Enough competent staff (education, training, skills and | Maintenance of professional profiles of |

| | | |
|---|---|---|
| | experience) are assigned to perform clinical trials oversight activities. | staff responsible for clinical trials including members of CSC. |

3. Accordingly, Draft Clinical Studies Committee (CSC) Operational Manual prepared & after approval of Chairman CSC forwarded to CEO-DRAP for approval. CEO-DRAP forwarded the draft to QMS-Section for review, QMS-Section reviewed & reworked the draft & suggested that, the draft should be approved by CSC prior to submission before CEO-DRAP for approval.

4. Draft Clinical Studies Committee (CSC) Operational Manual was also shared with CSC members through email on 30th September 2021 for review & comments. Draft CSC Operational Manual is attached as **(Annex-IV).**

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

**Decision:**

*The CSC after deliberation / detailed discussion decided to approve the CSC Operational Manual* **(Annex-IV),** *for achievement of WHO-Global Benchmarking Tools level-III.*

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**AGENDA ITEM XIII: GUIDENCE DOCUMENT ON GCP COMPLIANCE INSPECTIONS & LIST OF TRAINING PROGRAMME FOR GCP INSPECTORATE. F. No.08-39/2021-DD (PS)**

Reference to the Institutional Development Plans (IDPs) assigned to GBT-Teams. GBT-Teams constituted vide letter number F.No.06-04/2021-Admn-I dated 17th August 2021.

2. In the scheduled meeting of Clinical Trial Oversight GBT-Team, dated 27th September 2021, reviewed the list of training programme for GCP inspectorate after its nomination / notification & guidance document is prepared for GCP compliance inspection/audits according to following IDPs.

| Sr. No. | Tasks Assigned as per IDP | Nature of Activity |
|---|---|---|
| **1.** | CT02.01: There is a defined structure with clear responsibilities to conduct clinical trial oversight activities | Establishment of GCP Inspectorate to ensure regular monitoring of conductance of clinical trials. |
| 2. | CT03.03: Training plan developed, implemented and updated at least once a year | Training for GCP Inspectorate for clinical trials oversight |

3. Following draft documents were forwarded to QMS section for review vide file bearing number F.No.08-39/2021 DD(PS):

i. Guidance on GCP Compliance Inspection (**Annex-V**)
ii. Good Clinical Practice (GCP) Inspectorate Training Program (**Annex-VI**)

4. The draft documents also shared with CSC members through email on 30th September 2021 for review & comments.

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

**Decision:**

*The CSC after deliberation / detailed discussion decided to approve the following guidance documents for achievement of WHO-Global Benchmarking Tools level-III*

i. Guidance on GCP Compliance Inspection (**Annex-V**)
ii. Good Clinical Practice (GCP) Inspectorate Training Program (**Annex-VI**)

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**AGENDA ITEM XIV:**

**RATIFICATION FOR CHANGE OF APPLICANT AND LICENCE FOR LICENSEE NAME IN THE LICENCE DUE TO RETIREMENT OF APPLICANT FOR APPLICATION TO ACT AS CLINICAL TRIAL SITE, AT NATIONAL INSTITUTE OF CARDIOLOGY (NICVD) KARACHI. F. No.15-15/2021 DD (PS)**

It is submitted that, application for approval of M/s National Institute of Cardiovascular Diseases, Rafique (H.J) Shaheed Road, Karachi, to act as Clinical Trial Site was submitted by **Professor Syed Nadeem Hassan Rizvi**, the then Director Interventional Cardiology Program & Cath Lab, M/s National Institute of Cardiovascular Diseases, Rafique (H.J) Shaheed Road, Karachi.

2. At the time of issuance of licence it was informed by **Prof. Nadeem Qamar,** Executive Director & Prof. of Cardiology, M/s NICVD, Karachi vide letter number Nil, dated 23rd September 2021 that, Professor Syed Nadeem Hassan Rizvi has been retired from the post of Director Interventional Cardiology Program & Cath Lab, M/s NICVD, Karachi & **Professor Tahir Saghir, holding CNIC:42101-0226457-3 is new incumbent &** Head Department of Cath Lab & Interventional Programme, NICVD, Karachi.

3. **Prof. Nadeem Qamar,** Executive Director & Prof. of Cardiology, M/s NICVD, Karachi further requested to grant the licence for M/s NICVD to act as Clinical Trial Site in the name of **Professor Tahir Saghir,** Head Department of Cath Lab & Interventional Programme, NICVD, Karachi.

4. Accordingly, licence number CTS-0074 is granted for M/s NICVD, Karachi to act as clinical trial site in the name of **Professor Tahir Saghir,** Head Department of Cath Lab & Interventional Programme, NICVD, Karachi, on 24th September 2021.

5. **Submitted for ratification & for information of CSC.**

**Decision**

*CSC in light of briefing by Secretary CSC on the issue decided to approve & ratify the issuance of licence in the name of **Professor Tahir Saghir,** Head Department of Cath Lab & Interventional Programme, M/s National Institute of Cardiovascular Diseases, Rafique (H.J) Shaheed Road, Karachi.*

**AGENDA ITEM XV:**

**INVESTIGATION OF SERIOUS ADVERSE EVENT WITH DRUG IBREXAFUNGERP OCCURRED DURING TRIAL TITLED, "OPEN-LABEL STUDY TO EVALUATE THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SCY 078 (IBREXAFUNGERP) IN PATIENTS WITH CANDIDIASIS INCLUDING CANDIDEMIA, CAUSED BY CANDIDA AURIS".F.No.03-15/2019 DD (PS)**

In reference to letter number nil, dated 23rd February 2021, submitted by Principal Investigator of subject clinical trial. Wherein P.I. submitted six monthly progress report of subject trial.

2. Progress of the trial is as follows:

| Aug-2020 to Feb 2021 | | | | |
|---|---|---|---|---|
| Principal Investigator's Name/Site No. | Number of subjects screened | Screen failed | Patients enrolled | Serious adverse event update |
| Dr. Syed Faisal Mahmood / PK 060 | 16 | 15 | 01 | 02 (Diarrhea-rehospitalization & death) |

3. In the submitted report it is observed that there are 02 deaths occurred due to SAEs. In this regard Chairman CSC nominated following expert members to find out root cause of death of the trial subjects:

i. Prof. Ejaz A. Vohra, MBBS, MD (Medicine), FRCP (Medicine) General Physician, Dr, Ziauddin Hospital North Nazimabad, Karachi.
ii. Prof. Abdul Basit, MBBS, FRCP, Baqai Medical University, Karachi.
iii. Dr. Aamir Jaffary, Sindh Institute of Urology & Transplantation (SIUT), Karachi.

4. Dr. Saif Ur Rehman Khattak, Director CDL-Karachi, in reply of this Division letter bearing number F.No.09-06/2021 DD (PS) dated 21st June 2021. Submitted investigation report **(Annex-VII)** conclusion of the investigation is as follows:

***Conclusion:***

*Keeping in view the review of the study protocol, related documents such as informed consent, CRF, Lab tests, medication details, monitoring details, adverse events monitoring records, record of health issues and hospitalization of the patient, technical discussion and deliberations of the personnel involved in the trial, opinion of the principal investigator and ethics review committee of Agha Khan University Hospital, the panel has substantial evidence to conclude as under:*

*i. That the subject was a diagnosed case of duodenal adenocarcinoma and abdominal tuberculosis. Her medical history also included obstructive uropathy and gastric outlet obstruction along with urinary /bladder candidiasis or Candida auris cystitis which was treated with SCY-078 Ibrexafungerp tablets (the drug under the subject clinical trial) and at end of the treatment urinary cultures showed no growth for candida auris. Considering that the subject had underlying metastatic duodenal adenocarcinoma and was on chemotherapy, she developed multiple complications including Pneumonia due to Stenotrophomonas and Mucormycosis, Hepatic encephalopathy and severe Candidemia. These complications resulted in pneumonia, abdominal pain, systemic candida, hepatic*

*encephalopathy, and vomiting hence have been described as not related to the study drug by the principal investigator and the sponsor.*

ii. *The investigation panel also has strong opinion that the SAE reported is not related to the drug under trial. Relapse of the infection and subsequent death of the patient is due to complications of her underlying health conditions. Further, she was given appropriate and possible supportive care by the hospital, however, her health conditions worsen with time and finally resulted in loss of life.*

5. Investigation report was also shared with CSC members through email on 01st October 2021 for review & comments.

6. **Submitted for perusal, discussion and guidance/decision of CSC.**

**Decision:**

*The investigation report of the panel placed before the CSC for information was unanimously endorsed by the Committee.*

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**AGENDA ITEM XVI:**

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

Application is submitted by Dr. Faisal Mahmood (PI) dated 07th September 2021. Wherein application principal investigator of subject trial submitted progress reports & as trial duration expired PI asked for extension in the trial duration for another year.

2. It is submitted that, the trial was approved on 26th August 2020 for 132 days for recruitment of 15 subjects in Pakistan. The trial duration expired on 05th January 2021.

3. Applicant submitted progress report of "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" as follows:

**Protocol Number:** SCY-078-305
**Sponsor:** SCYNEXIS, Inc 101 Hudson Street, Suite 3610 New Jersey City, NJ 07302
**Principle Investigator:** Dr. Faisal Mahmood
**Centre:** The Aga Khan University
**Study Recruitment and Activity**
Target Recruitment: 15
Total # of subjects Pre-Screened: 34
Total # of subjects Enrolled: 02
Total # of Adverse Events:30
Total # of subjects who had Serious Adverse Events:02

4. After initial recruitment following shortcomings observed in the extension application:

i. Application for extension in trial need to be submitted with original signatures in original.

ii. Prescribed fee of Rs.25000/- shall be submitted in miscellaneous head in DRAP account.
iii. IRB approval for extension in the trial is not provided.
iv. NBC approval for extension & amendment in Investigator's Brochure of the trial is not provided.
v. All correspondence from Principal Investigator received to Division of Pharmacy Services DRAP with scanned signatures, in future all correspondence shall be done with DRAP with original signatures, otherwise no action will be taken.

5. Accordingly, shortcomings communicated to applicant vide letter bearing number F.No.03-15/2019 DD (PS) dated 06th October 2021 but response is awaited yet.

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

7. Dr. Faisal Mahmood (PI) joined the meeting in-person & briefed the Committee regarding need of extension & answered the questions raised by the CSC members.

**Decision:**

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

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**AGENDA ITEM XVII:**

**REQUEST FOR APPROVAL AND REGISTRATION OF BIOEQUIVALENCE STUDY OF DELANZO™DR 60MG (DEXLANSOPRAOLE) CAPSULE OF M/S SAMI PHARMACEUTICALS (PVT) LTD WITH DEXILANT® 60MG (DEXLANSOPRAOLE) CAPSULE. F. No. 14-02/2020 DD (PS)**

The subject application for approval of BA/BE Studies was discussed in the 19th CSC meeting held on 12th February 2021 & CSC decided as follows:

*The CSC after detailed deliberation decided to approve the BA/BE Study titled "Bioequivalence Study of Delanzo™ DR 60mg (Dexlansopraole) Capsule of M/s Sami Pharmaceuticals (Pvt) Ltd with Dexilant® 60mg (Dexlansopraole) Capsule". However, applicant will provide details of reference product (i.e. CoPP & GMP certificate) & other evident documents for import of reference product, as per the Bio-Study Rules 2017 and reference standard may be any stringent regulatory authority / innovator product.*

2. The decision of the CSC communicated to the applicant vide this office letter bearing number F.No.16-19/2021 DD (PS), dated 26th February 2021, with the advice to submit details of reference product (CoPP & GMP Certificate) along with documents of reference product.

3. The applicant vide their reply dated 06th May 2021 disclosed that, innovator drug (reference product) will be from M/s Takeda Pharmaceutical U.S.A. However, the applicant again submitted reply dated 21st May 2021 & informed that, reference/innovator drug to be used in the study is manufactured by M/s Takeda Pharmaceutical Company, Limited, Japan and a copy of pack specimen was also submitted in this regard.

4. In the light of decision of CSC and as per form-IIA of the Bio-Study Rules, the applicant shall furnish COPP and GMP certificate of the reference product and the purposed label of reference product also need to be provided by the applicant that will reflect the necessary information about the investigational product i.e. its Batch # / Lot #, manufacturing date, expiry date and manufacturer name etc., from traceability point of view.

5. The procurement of investigational/reference product from any pharmacy as evident in the case through personal baggage is neither ethical nor legal and shall not be allowed as per international practices, guidelines / standards. It is the sole responsibility of the sponsor / PI to manage the import of reference product/investigational drug as per protocol to be used in BE study in compliance to the Drugs (Import & Export) Rules 1976 framed under the Drug Act 1976.

6. Prof. Dr. Raza Shah (PI) informed that, it is not possible for them to submit CoPP & GMP of the manufacturer of reference product. Further informed that, their representative has been purchased Dexilant 60mg Capsules the reference product from M/s Aqua Pharmacy, Dubai & only copy of purchase receipt is provided.

**7.** Dr. Raza Shah, again forwarded an application on 01st October 2021. Wherein application is on "**Choice of comparator in conducting bioequivalence studies in Pakistan**".

8. Applicant/PI submitted clarification/requirements for comparator product reproduced as follows:

*This is with reference to the WHO guidelines for the selection of comparator for the Bioequivalence studies which is enclosed to this letter. On page 188 the WHO offers six option for the choice of comparator and choice number 2 of the guidelines of the WHO read as "National market leader product for which a national marketing authorization has been granted". This clearly shows that WHO do not advise against using a product marketed in Pakistan as comparator for Bioequivalence studies. I am requested the following*

*I) Allow us to purchase comparator product in the light of WHO options for comparator available in the below link and enclosed document for your reference. (https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex8-TRS992.pdf)*

*II) The comparator product is purchased from the open market so it is impossible to provide COPP and GMP certificate of comparator product as the company preparing the comparator do not have any interest in the Clinical trial. Neither they are obligated to provide these certificates which is ultimately discouraging the pharmaceutical industries in conducting the clinical trials in Pakistan.*

9. Applicant also provided a copy of ***"Annex 8 Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products"***. (**Annex-VIII**.)

10. Chairman CSC discussed the matter & proposed that the matter should be placed before CSC, to find a way forward to clarify the requirements of CoPP & GMP Certificates for comparator product.

11. WHO-Guidance document (*Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products*) shared with CSC members through email on 06th October 2021 for review & comments.

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

13. Prof. Dr. Raza Shah joined the meeting through Zoom & briefed the Committee regarding difficulties faced during arrangement for CoPP & GMP certificate. Further requested for exemption of CoPP/GMP Certificate for reference products.

14. Secretary CSC appraised the Committee that, the applicant in their reply dated 06th May 2021 disclosed that, innovator drug (reference product) will be from M/s Takeda Pharmaceutical U.S.A. However, the applicant again submitted reply dated 21st May 2021 & informed that, reference/innovator drug to be used in the study is manufactured by M/s Takeda Pharmaceutical Company, Limited, Japan and a copy of pack specimen was also submitted in this regard by applicant. In the light of decision of CSC and as per Form-IIA of the Bio-Study Rules, the applicant should furnish COPP and GMP certificate of the reference product and the proposed label of reference product also need to be provided by the applicant that will reflect the necessary information about the investigational product i.e. its Batch # / Lot #, manufacturing date, expiry date and manufacturer name etc, from traceability point of view. The procurement of investigational/reference product from any pharmacy as evident in the case through personal baggage is neither ethical nor legal and shall not be allowed as per international practices, guidelines / standards. It is the sole responsibility of the sponsor / PI to manage the import of reference product/investigational drug as per protocol to be used in BE study in compliance to the Drugs (Import & Export) Rules 1976 framed under the Drug Act 1976.

15. It is further proposed by the Secretary CSC that, PI may amend the study protocol to change the source of reference product & its procurement from some GMP Compliant manufacturer under the Drugs (Import & Export) Rules 1976. The PI/Sponsor should make efforts to arrange the reference drug for the study and the rule provisions need to be complied with.

16. Prof. Brig. (R), Muzammil Hassan Najmi., Dr. Faiza Bashir, Farhana Badar & other members also endorsed that applicant should provide the CoPP & GMP Certificate as defined under prerequisites as per Bio-Study Rules. Chairman CSC submitted that the applicant is facing much problems for procurement & arrangement of CoPP & GMP Certificates, even their representative was investigated by the police of Germany.

**Decision:**

*The Chairman CSC constituted a sub-committee comprising of following members in light of deliberation / detailed discussion by the CSC :*

i. *Dr. Abdur Rashid, Chairman CSC, Director Pharmacy Services Division.*
ii. *Prof. Brig. (R), Muzammil Hassan Najmi, Member CSC & Professor of Pharmacology, Foundation University, Islamabad.*
iii. *Prof. Nadeem Irfan Bukhari, Member CSC & Professor of Bio-Pharmaceutics & Pharmacokinetics, University of Punjab, Lahore.*
iv. *Dr. Farhana Badar, Biostatistician & Epidemiologist, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.*

*The sub-committee shall evaluate the matter as provided under the Bio-Study Rules & in accordance with international standards/guidelines & practices & submit its report on the issue, which shall be placed before the CSC in its next meeting.*

**AGENDA ITEM XVIII:**

**REQUEST FOR APPROVAL AND REGISTRATION OF BIOEQUIVALENCE STUDY OF MOFEST® (MOXIFLOXACIN) 400MG TABLET OF M/S SAMI PHARMACEUTICALS (PVT) LTD WITH AVELOX® (MOXIFLOXACIN) 500MG TABLET OF M/S BAYER PAKISTAN.MOFEST-BA/BE STUDIES-ICCBS. F. No. 14-04/2020 DD (PS)**

The subject application for approval of BA/BE Studies was discussed in the 19th CSC meeting held on 12th February 2021 & CSC decided as follows:

> *The CSC after detailed deliberation decided to approve the BA/BE Study titled "Bioequivalence Study of Mofest® (Moxifloxacin) 400mg Tablet of M/s Sami Pharmaceuticals (Pvt) Ltd with Avelox® (Moxifloxacin) 500mg Tablet Of M/s Bayer". However, applicant will provide details of reference product (i.e. CoPP & GMP certificate) & other evident documents for import of reference product, as per the Bio-Study Rules 2017 and reference standard may be any stringent regulatory authority / innovator product*

2. The decision of the CSC communicated to the applicant vide this office letter bearing number F.No.16-19/2021 DD (PS), dated 26th February 2021, with the advice to submit details of reference product (CoPP & GMP Certificate) along with documents of reference product.

3. The applicant vide their reply dated 06th May 2021 disclosed that, innovator drug (reference product) will be from M/s Bayer Healthcare Pharmaceuticals U.K. However, the applicant again submitted reply dated 21st May 2021 & informed that, reference/innovator drug to be used in the study is manufactured by M/s Bayer Pharma AG, Germany and a copy of pack specimen was also submitted in this regard by applicant.

4. In the light of decision of CSC, the applicant shall furnish CoPP and GMP certificate of the reference product as per form-IIA of the Bio-Study Rules and the purposed label of reference product also need to be provided by the applicant that will reflect the necessary information about the investigational product i.e. Batch # / Lot #, manufacturing date, expiry date and manufacturer name etc., from traceability point of view.

5. The procurement of investigational/reference product from any pharmacy will be neither ethical nor legal and shall not be allowed as per international practices, guidelines / standards. It is the sole responsibility of the sponsor / PI to manage the import of reference product/investigational drug as per protocol to be used in BE study in compliance to the Drugs (Import & Export) Rules 1976 framed under the Drug Act 1976.

6. Applicant informed that there is no possibility to provide CoPP & GMP certificate of the reference product. Further requested that as reference product is already approved by FDA, the reference product will be purchased from the market of any stringent regulatory authority & will provide the purchase & shipment record of the reference /innovator product with final study report.

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

8. Discussion as per previous case.

**Decision:**

*The CSC after deliberation / detailed discussion the Chairman CSC constituted sub-committee comprising of following members:*

*i. Dr. Abdur Rashid, Chairman CSC, Director Pharmacy Services Division.*

ii. *Prof. Brig. (R), Muzammil Hassan Najmi, Member CSC & Professor of Pharmacology, Foundation University, Islamabad.*
iii. *Prof. Nadeem Irfan Bukhari, Member CSC & Professor of Bio-Pharmaceutics & Pharmacokinetics, University of Punjab, Lahore.*
iv. *Dr. Farhana Badar, Biostatistician & Epidemiologist, Shaukat Khanum Memorial Cancer Hospital & Research Center, Lahore.*

*The sub-committee shall evaluate the matter as provided under the Bio-Study Rules & in accordance with international standards/guidelines & practices & submit its report on the issue, which shall be placed before the CSC in its next meeting.*

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**AGENDA ITEM XIX:**

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

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

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

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

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

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

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

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

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

**Decision:**

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

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**AGENDA ITEM XX:**

**REQUEST FOR USE OF DRUGS BETWEEN TWO APPROVED TRIALS END-TB AND ENDTB-Q DUE TO SUPPLY CHANGE DISRUPTION. F. No.03-04/2019-DD (PS) & F. No.03-17/2019-DD (PS) RESPECTIVELY.**

Application submitted by Dr. Naseem Salahuddin, P.I. End-TB & End-TB Q Clinical Trial, wherein applicant submitted following request:

a. *Due to the COVID-19 pandemic, supply chain activities have been affected worldwide. This has led to delays in order processing and clearance of medicines. However, such delays in procurement and import of medicines can hinder and halt dispensation and distribution of lifesaving medications, cither for routine use or for ongoing research.*

b. *In this vein, for the endTB clinical trials i.e., endTB and endTB-Q - approved by National Bioethics Committee (NBC) and DRAP - the lead time for drug delivery from MSF logistique (supplier of trial medicines) to Pakistan has been increased from four to six months since the start of the pandemic. The endTB trial team are working to mitigate any possibility of drug stock out. However, we foresee risks in potential stock out for a few trial medicines at the start of June 2021. 3. It is important to note that anti-TB medicines used in both endTB and endTB-Q clinical trials are the same. The only difference related to drugs between the trials is the combination of regimen used in each trial. Therefore, in order to avoid potential stock out and treatment interruption due to unavailability of medicines, we should be able to use the medicines available in endTB stock for endTB-Q patients and vice versa since the source, composition and strength is the same.*

c. *In light of the above, we would like to request DRAP to allow the use of medicines between the two trials in case of stock out or such emergency situations, hence not compromising on the safety of the trial participants.*

2. Application was placed before CSC in its 25th meeting held on 28th April 2021 & the Committee decided as follows:

*The CSC after detailed deliberation decided to defer the case, latest study protocol of both trials (i.e. endTB & endTB-Q) will be shared with CSC members for further detailed deliberation & review.*

3. Accordingly, decision communicated to applicant but applicant not provided any soft copies yet, further after many communications Dr. Naseem Salahuddin, Principal Investigator of endTB Clinical Trial, The Indus Hospital & Health Network, Karachi again submitted application along with following attachments:

i. Prescribed fee for miscellaneous application submitted vide challan number 95480904127, dated 15th September 2021 verified online.
ii. Ethical approval from Institutional Review Board (IRB) of Indus Hospital & Health Network (formerly The Indus Hospital, Karachi) dated 18th August 2021.
iii. National Bioethics Committee (NBC) approval Ref:No.4-87/NBC-362-Amend/21/1563 & 1562 dated 03rd June 2021. NBC approval is for use of drugs between two approved trials endTB and endTB-Q due to supply change disruption.

4. Applicant also provided inventory report of the endTB & endTB-Q Clinical Trial **(Annex-X)** which is also shared with expert CSC members through email on 01st October 2021 for review.

5. After initial scrutiny following shortcomings observed:

i. Application for use of IMPs between endTB & endTB-Q trials are not signed in original by the PI.

6. It is submitted that, uninterrupted & continuous supply of Investigational Medicinal Products (IMPs) is the sole responsibility of Sponsor & there is no provision in the Bio-Study Rules for exchange of IMPs between two different Clinical Trials.

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

8. Dr. Naseem Salahuddin, is the Principal Investigator of endTB & endTB-Q Clinical Trials. So, before discussion she left the meeting due to conflict of interest & Dr. Sadia Ausim representative of PI & Sponsor joined the meeting through Zoom & briefed the Committee regarding use of IMPs/Drugs Between Two Approved Trials end-TB and endTB-Q Due to Supply Change Disruption & answered the questions raised by the CSC members.

***Decision:***

*CSC after detailed deliberation decided to reject the request of the PI of the trial regarding use of IMPs/Drugs between two approved trials end-TB and endTB-Q due to supply change disruption, as uninterrupted & timely supply of the Investigational Medicinal Product (IMPs) is responsibility of the trial sponsor. Therefore, use of IMPs between two separate Clinical Trials (i.e. endTB & endTB-Q) can't be allowed.*

**AGENDA ITEM XXI:**

**APPLICATION FOR APPROVAL OF AMENDMENT OF PROTOCOL & INVESTIGATOR'S BROCHURE FOR CLINICAL TRIAL TITLED "A MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PHASE-II CLINICAL TRIAL TO EVALUATE THE EFFICACY & SAFETY OF CBP-307 IN SUBJECTS WITH MODERATE TO SEVERE ULCERATIVE COLITIS (UC)"F.NO.03-59/2021 DD (PS).**

Application is from Dr. Saeed Hamid (CNIC 42000-0516220-5), Director, Clinical Trial Unit, Professor & Consultant Gastroenterologist, Aga Khan University Hospital, Karachi, dated 28th June 2021, along with a fee of Rs.25000/- deposited vide challan no.7130454542 dated 25th June 2021. Wherein request has been made for amendments in already approved protocol of clinical trial titled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase-II Clinical Trial to Evaluate the Efficacy & Safety Of CBP-307 in Subjects with Moderate to Severe Ulcerative Colitis (UC)".

2. Applicant provided following documents along with softcopies received through email:

i. Application along with prescribed fee.
ii. AKUH-IRB approval for amendment of protocol version from 5.0 to 6.0.
iii. NBC- amendment approval letter reference No.4-87/NBC-591/21/1575, dated 11th June 2021.
iv. Amended protocol version 6.0 along with its summary.
v. Amended Investigator's Brochure version 6.0 along with its summary.
vi. Revised Informed Consent Form (English & Urdu with translation certificate)(Page 922-921/Corr.)
vii. Updated Inflammatory Bowel Disease Questionnaire (IBDQ) (English & Urdu with translation certificate)(Page 1040-921/Corr.)
viii. NBC- protocol amendment approval letter reference No.4-87/NBC-591/21/1575, dated 16th June 2021. (Page 1056-1058/Corr.)

3. Summary of changes is as follows:

**A. Summary of Changes for CBP-307 Investigator Brochure V6.0**

| Chapter | Page No. | Additional Content (V6.0, Dec 15, 2020) |
|---|---|---|
| 6.4.3 Contraindication | 132 | Adding the following content:<br>The following conditions will be contraindicated to treatment with CBP- 307:<br>• Recent myocardial infarction<br>• Unstable angina<br>• History of stroke or transient ischemic attack<br>• Heart failure class III or IV<br>• History of Mobitz Type II 2nd degree or 3rd degree AV block<br>• Sick sinus syndrome |

| | | |
|---|---|---|
| | | • Prolonged QT interval arrythmias requiring treatment with Class Ia or III anti-arrhythmic drugs<br>• Pregnancy |

**B. Protocol amendment (V6.0) Summary of Changes**

Summary of changes is attached. (**Annex-XI**)

4. Technical documents (Investigator's Brochure, amended protocol & Summaries) shared with CSC members through email on 06th October 2021 for review & comments.

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

6. Dr. Saeed Hamid, Director CTU Aga Khan University Hospital, Karachi joined the meeting online & briefed the Committee regarding amendments in the study protocol and answered the questions raised by the CSC members.

**Decision:**

*The CSC after deliberation / detailed discussion decided to approve the proposed amendments in the protocol version 6.0 of already approved clinical trial titled "A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Phase-II Clinical Trial to Evaluate the Efficacy & Safety of CBP-307 in Subjects with Moderate to Severe Ulcerative Colitis (UC)".*

**AGENDA ITEM XXII:**

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

Progress report of the subject clinical trial is from Dr. Saeed Hamid (PI), Director, Clinical Trial Unit, Professor & Consultant Gastroenterologist, Aga Khan University Hospital, Karachi, dated 13th September 2021.

2. Study progress report is as follows:

**i. Progress report: (Mar-2021 to Aug-2021)**

| **Principal Investigator Name/Site No.** | **Total Number of Subjects Screened** | **Total Number of Subjects Screen failed** | **Total Number of patients randomized** | **Serious Adverse Events** (Mar-2021 to Aug-2021) |
|---|---|---|---|---|
| Dr. Saeed Hamid /2125 | 05 | 02 | 02 | No SAEs. |

**ii. Protocol deviations:**

| Subject ID | Visit ID | Deviation Description | Date of Deviation | Category |
|---|---|---|---|---|
| 2151001 | Week 1 Day 5 | On day 5, subject number2151001 has received medication from kit number 2A01545 (dispensed on day 1) instead of kit number 2B01780 (dispensed on day 5). The subject was dispensed two bottles from kit number 2401545 which contain 1 capsule/bottle (CBP-307 0.05m9 or Placebo). However, this does not change the required dosing regimen (i.e., subject should receive a cumulative dose of 0.1m9 or placebo on day 5) as kit number 2801780 contains 2 capsules/bottle (2 placebo capsules or 2 CBP-307 0.05m9 capsules). | 17 Aug 2021 | Minor |
| 2151002 | Week 1 Day 5 | On day 5, subject number 2151002 has received medication from kit number 2A01542 (dispensed on day 1) instead of kit number 2801783 (dispensed on day 5). The subject was dispensed two bottles from kit number 2A01542 which contains 1 capsule/bottle (CBP-307 0.05m9 or Placebo). However, this does not change the required dosing regimen (i.e., subject should receive a cumulative dose of 0.1 mg or placebo on day 5) as kit number 2801783 contains 2 capsules/bottle (2 placebo capsules or 2 CBP-307 0.05m9 capsules). | 17 Aug 2021 | Minor |

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

4. Dr. Saeed Hamid, Director CTU Aga Khan University Hospital, Karachi joined the meeting online & answered the questions raised by the CSC members.

**Decision:**

*"The Progress report/Serious Adverse Event report in the trial comprising of minor adverse events placed before CSC for information was endorsed by the Committee".*

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**AGENDA ITEM XXIII:**

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

Application is from Dr. Saeed Hamid (PI) & Director, Clinical Trial Unit, Aga Khan University, Karachi, dated 03rd August 2021, wherein F.R. is a 6 monthly progress report (Jan-2021 to June-2021). The report is as follows:

| Principal Investigator Name/Site | Total Number of subject screened | Total Number of subject screens failed | Total number of patients Randomized | Serious Adverse events (Jan-2021 to Jun-2021) |
|---|---|---|---|---|
| Dr. Saeed Hamid/420 | 70 | 27 | 36 | 011-420-0015 Acute appendicitis |

2. Further applicant applied for extension in trial duration as the subject trial will be expired on 12th November 2021. PI informed that they have enrolled 45 patients out of 80 as per approved license No. CT0002 and they are expecting last patient's enrollment till January 2022 and last patient last visit is expected in July 2023. Import licence has been granted on 12th December for below mentioned quantities of IMPs:

| | Kits Approval | Kits Imported Yet | Remaining kits |
|---|---|---|---|
| Tablets Lonafarnib and Ritonavir (Active/ Placebo) | 960 | 386 | 960-386= 574 |
| PEG IFN-alfa-2a | 240 | 186 | 420 - 186= 234 |

3. Applicant provided following documents:

i. Copy of Clinical Trial Registration Certificate.
ii. Copy of Import Licence for IMPs.
iii. Copy of Six-Monthly Progress Report.
iv. Copy IRB/ERC extension approval for one year, dated 17th February 2021. Issued by IRB/ERC of Aga Khan University Hospital Karachi.
v. Copy NBC extension approval letter Reference Number 4-87/NBC-384-Y3-Extension/21/1403, dated 24th March 2021.
vi. Fee of Rs.25000/- for miscellaneous applications also submitted vide challan number 6857069156, dated 04th October 2021.

4. Progress report was shared with CSC experts through email on 08th October 2021 for review. No comments received from the members

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

6. Dr. Saeed Hamid, Director CTU Aga Khan University Hospital, Karachi joined the meeting online & briefed the Committee regarding amendments in study protocol and answered the questions raised by the CSC members.

**Decision:**

*The CSC after deliberation / detailed discussion decided to approve the application for extension for one year for already approved clinical trial titled "A Phase-III, Matrix Design, Partially Double Blind, Randomized Study of the Efficacy and Safety of 50mg Lonafarnib / 100mg Ritonavir BID with & without 180mcg PEG IFN-Alfa-2a for 48 Weeks, Compared with PEG IFN-Alfa-2a Monotherapy and Placebo Treatment in Patient Chronically Infected with Hepatitis Delta Virus Being Maintained on Anti-HBV Nucleos (T) ide Therapy (D-LIVR)".*

**AGENDA ITEM XXIV:**

**AN INTERNATIONAL, MULTI-CENTER, CONTROLLED, RANDOMIZED CLINICAL TRIAL TO EVALUATE RIFAMPICIN 1200MG AND 1800MG DAILY IN THE REDUCTION OF TREATMENT DURATION FOR PULMONARY TUBERCULOSIS FROM 06 MONTHS TO 04 MONTHS.**

Application is from Dr. Bushra Jamil, P.I. RIFASHORT Trial, Department of Medicine, The Aga Khan University, Karachi, dated 26th August 2021, wherein application is a 6 monthly progress report.

2. The progress report is as follows:

| Principal Investigator Name/Site | Patients Pre-Screened | Patient Screened | Screen Failure | Withdrawals | Patients Enrolled/ Randomized | SAE Updates |
|---|---|---|---|---|---|---|
| Dr. Bushra Jamil/AKU420 | 507 | 32 | 02 | 05 | 30 | 2 SAEs in this reporting period. 1 Pregnancy (Notifiable Adverse Event according to protocol) |

3. Progress report was shared with CSC experts through email on 08th October 2021 for review. No comments received from the members

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

**Decision:**

*The Serious Adverse Event report in the trial placed before CSC for information was endorsed by the Committee.*

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**AGENDA ITEM XXV:**

**PROGRESS REPORT OF CLINICAL TRIAL TITLED "PREVENTION OF METRNAL & NEONATAL DEATH/INFECTIONS WITH A SINGLE ORAL DOSE OF AZITHROMYCIN IN WOMEN IN LABOR (IN LOW- & MIDDLE-INCOME COUNTRIES), A RANDOMIZED CONTROLLED TRIAL.F.No.03-09/2019 DD (PS)**

Application is from Prof. Dr. Sarah Saleem, Professor, Principal Investigator, A-Plus Trial, Department of Community Health Sciences, Aga Khan University, dated 31st May, 2021, wherein FR is a progress report of subject trial from Oct-2020 till date.

2. Brief report is as follows:

| Reporting period: Oct-2020 – to date | | | | | | |
|---|---|---|---|---|---|---|
| P.I. | No. of subject screened | Eligible cases | Ineligible cases | Refuse to participate | Patients randomized | Adverse event |
| Prof. Dr. Sara Saleem | 2096 | 1181 | 915 | 38 | 1125 | 05 |

3. It is submitted that, application is with scanned signatures. PI may be asked to submit reports & all correspondence with original signatures. Accordingly, DFA is placed for further perusal.

4. Progress report was shared with one CSC member (Dr. Aamir Jaffrey) as per directions through email on 07th October 2021 for review & comments. No comments received from

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

**Decision:**

*The CSC was appraised about the Progress Report submitted by the PI of the trial that was endorsed by the Committee after perusal.*

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**AGENDA ITEM- XXVI:**

**AMENDMENT IN PROTOCOL FROM 1.1 TO 1.2 AND ICF VERSION 1.3 TO 1.4 FOR CLINICAL TRIAL TITLED AS A PHASE III RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED CLINICAL TRIAL IN 18 YEARS OF AGE AND ABOVE TO DETERMINE THE SAFETY AND EFFICACY OF ZF2001, A RECOMBINANT NOVEL CORONA VACCINE (CHO CELL) FOR PREVENTION OF COVID-19. (F.No.03-52/2021 DD (PS).**

Application is from Sheikh Asim Munir, Project Lead, DRK Pharma Solutions, Lahore, dated 7th July, 2021, along with a fee of Rs.25000/- deposited vide Challan No.0298004026 dated 21st June 2021. Wherein request has been made for amendments in already approved protocol of clinical trial titled "Amendment in Protocol from Version 1.1 to 1.2 And ICF Version 1.3 to 1.4 For Clinical Trial Titled as A Phase III Randomized, Double Blind, Placebo Controlled Clinical Trial In 18 Years of Age and Above to Determine the Safety and Efficacy of ZF2001, A Recombinant Novel Corona Vaccine (CHO Cell) For Prevention Of COVID-19.".

2. Applicant provided following documents:

x. Application along with prescribed fee.
xi. IRB approval for amendment of protocol version from Protocol 1.1 and ICF 1.3 to Protocol 1.2 and ICF 1.4.
xii. NBC- amendment approval letter reference No.4-87/NBC-COVID-57/21/46, dated 13th July, 2021.
xiii. Amended protocol version 1.2 along with its summary.
xiv. Amended Investigator's Brochure version 1.2.
xv. Revised Subjects Screening Form.
xvi. Revised Patient Information Sheet.
xvii. Revised Informed Consent Form (English & Urdu)

3. Subject clinical trial (Protocol version 1.1) was amended in 29th meeting of CSC held on 5th August 2021.

4. Now the firm has requested for amendment in protocol from Version 1.1 and amended ICF i.e. Version 1.3 to Version 1.2 and amended ICF i.e. Version 1.4 for clinical trial titled "A phase III randomized, double blind, placebo controlled clinical trial in 18 years of age and above to determine the safety and efficacy of ZF2001, a recombinant novel corona vaccine (CHO cell) for prevention of covid-19".

**5. SUBMIITED FOR CONSIDERATION OF CSC**

**6.** Mr. Asim Munir, Project Manager, M/s DRK, Pharma Solution, Lahore with his team joined the meeting in-person & briefed the Committee regarding amendment in trial & answered the questions raised by the members.

**Decision:**

*The CSC after deliberation / detailed discussion decided to approve the proposed amendments in the protocol version 1.1 to 1.2 & ICF Version 1.3 to 1.4 of already approved clinical trial titled "A Phase III Randomized, Double Blind, Placebo Controlled Clinical Trial in 18 Years of Age and Above to Determine the Safety and Efficacy of ZF2001, A Recombinant Novel Corona Vaccine (CHO Cell) for Prevention of Covid-19".*

**AGENDA ITEM- XXVII:**

**APPLICATION FOR AMENDMENT IN ALREADY APPROVED CLINICAL TRIAL TITLED "A MULTICENTER, SEAMLESS, RANDOMIZED, THIRD-PARTY-BLIND CLINICAL TRIAL TO EVALUATE THE SAFETY & EFFICACY OF MEPLAZUMAB (INJECTION) IN ADDITION TO STANDARD CARE FOR THE TREATMENT OF COVID-19 IN HOSPITALIZED ADULTS" F.NO.03-54/2021 DD (PS).**

Application is from Dr. Nosheen Nasir (PI), Assistant Professor, Department of Medicine, Aga Khan University Hospital, Karachi, dated 04th October 2021. Wherein FR is a protocol amendment application in subject application.

2. Applicant provided following documents with application;

1) Initial DRAP Approval letter dated 31-MAR-2021 (Page 05-07/Corr.)
2) National Bioethics Committee (NBC) Approval letter for protocol Amendment (Page 09/Corr.)
3) National Bioethics Committee (NBC) Approval letter for Protocol Amendment (Page 10/Corr.)
4) Ethics Review Committee (ERC) Approval letter for Protocol Amendment 2 (Page 11-12/Corr.)
5) Ethics Review Committee (ERC) Approval Letter for Protocol Amendment 3 (Page 13/Corr.)
6) New informed Consent Form (ICF) document version 5.0(Page 14-26/Corr.)
7) Ethics Review Committee (ERC) Approval letter for the new Informed Consent Form (Page 27-28/Corr.)
8) Protocol Amendment 2 (Page 29-51/Corr.)
9) Protocol Amendment 3 (Page 52-75/Corr.)
10) Prescribed fee submitted vide challan number 5508358395 dated 05th October 2021 for miscellaneous applications. (Page 02/Corr.)

3. It is submitted that, the trial was approved on 31st March 2021 for recruitment of 100 subject for Stage-I & 50 subjects for Stage-II. The study duration for each subject was 84±7 days. As per approval the trial duration is expired, the PI may be asked for updated recruitment status.

4. Technical documents (Summary of amendments) were shared with expert CSC members through email on 11th October 2021 for review & comments.

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

6. Dr. Saeed Hamid, Director CTU Aga Khan University Hospital, Karachi joined the meeting online & briefed the Committee regarding amendments and answered the questions raised by the CSC members.

**Decision:**

*The CSC after deliberation / detailed discussion decided to approve the proposed protocol amendments 2 & 3 of already approved clinical trial titled "A Multicenter, Seamless, Randomized, Third-Party-Blind Clinical Trial to Evaluate the Safety & Efficacy of Meplazumab (Injection) in Addition to Standard Care for The Treatment of COVID-19 in Hospitalized Adults".*

*Further CSC decided to direct the PI to clarify the total duration of the Clinical Trial from the date of its approval.*

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**AGENDA ITEM XXVIII:**

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

Application is from Dr. Saeed Hamid, Director, Clinical Trial Unit, Professor & Consultant Gastroenterologist, Department of Medicine, Aga Khan University Hospital, Karachi, dated 13th September 2021, on prescribed Form-II along with a fee of Rs.200000/- deposited vide challan no.163956865900, dated 13th September 2021. Wherein request has been made for registration & approval of subject clinical trial, which will be carried out at Clinical Trial Unit, Aga Khan University Hospital Main Campus, Stadium Road, Karachi.

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

i. **Name of Investigational product, including all available names; trade, generic or INN name etc.:**
The investigational product used in this study is a Hepatitis C self-test kit: OraQuick® HCV Self-Test manufactured by OraSure Technologies Inc., USA. The OraQuick® HCV Rapid Antibody Test is prequalified by WHO for professional use (Index 10). The test uses oral fluid sample which will be obtained by the participant taking a swab from their gums. Instructions for use, with both English and Urdu translations have been attached (Index 3) As this HCV test is not approved for self-test use in Pakistan, all tests will be labelled as Research Use Only (RUO) and test results will not be used for patient management. E)

ii. **Purpose of trial defining the indication along with the anticipated cost of the project and sources of fund:**
In order to achieve the goal of elimination of Hepatitis C infection in Pakistan, the strategy of elimination needs to be increasingly directed towards case finding through mass screening in rural or peri-urban communities to identify and treat those not yet aware of their infection. The purpose of this study is to evaluate the acceptability and impact of a home-delivery HCV self- testing kit in the Malir district, Karachi division, Pakistan. The availability of self-testing has been shown to increase testing rates and testing acceptability in diverse populations around the world, in large part due to its convenience and privacy advantages. Self-testing with easy-to-use rapid diagnostic tests has been successfully used for diseases such as HIV.

iii. **Sponsor:** Foundation for Innovative New Diagnostics (FIND), Geneva, Switzerland.

iv. **Primary Objective of the study:**
To assess the impact of HCV self-testing home delivery on HCV antibody testing rates.

v. **Schedule of activities:** Baseline visit (randomization):
HCV antibody testing (either HCVST left with household or participant in control group attends nearby site, Memon Goth Hospital for testing)
**Month 1-2:**

1. Collection of testing results and survey on perceptions of testing process.
2. Referral of HCV antibody positive individuals for confirmatory testing and linkage to care.
3. Linking of data for RDT test Linking of data for RDT test (control group) and RNA test and treatment initiation (as applicable for intervention and control group) 4. Adverse Event (AE)/Serious Adverse Event (SAE) review 5. Cost data collection and analysis.

**Months 2-8:**

1. Referral of HCV antibody positive individuals for confirmatory testing and linkage to care.
2. Linking of data for RDT test Linking of data for RDT test (control group) and RNA test and treatment initiation (as applicable for intervention and control group) 3. Adverse Event (AE)/Serious Adverse Event (SAE) review.
4. Cost data collection and analysis.

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

| S. No. | Document | Remarks |
|---|---|---|
| 1 | Application on prescribed Form-II | Attached. |
| 2 | Prescribed processing fee | Fee of Rs.200000/- deposited vide challan no.163956865900, dated 13th September 2021 |
| 3 | Investigator Brochure (s) | Instead of Investigator's Brochure device (user manual) is attached. Investigator's Brochure as per ICH-GCP guidelines need to be provided. |
| 4 | Final protocol | Draft protocol is attached & the protocol is not signed.<br>Version 0.4<br>Protocol no.HC023<br>*Details regarding financing & insurance is not described in the protocol. |
| 5 | Informed consent and participant information sheet (Urdu to English) | Attached |
| 6 | List of participating countries | N/A |
| 7 | Phase of trial. | Phase of the study is not described, where as schedule of activities is provided as follows:<br>Baseline visit (randomization): HCV antibody testing (either HCVST left with household or participant in control group attends nearby site, **Memon Goth Hospital** for testing)<br>• Month 1-2:<br>1. Collection of testing results and survey on perceptions of testing process.<br>2. Referral of HCV antibody positive individuals for confirmatory testing and linkage to care.<br>3. Linking of data for RDT test Linking of data for RDT test (control group) and RNA test and treatment initiation (as applicable for intervention and control group)<br>4. Adverse Event (AE)/Serious Adverse Event (SAE) review.<br>5. Cost data collection and analysis |

| | | |
|---|---|---|
| | | • Months 2-8:<br>1. Referral of HCV antibody positive individuals for confirmatory testing and linkage to care.<br>2. Linking of data for RDT test Linking of data for RDT test (control group) and RNA test and treatment initiation (as applicable for intervention and control group) 3. Adverse Event (AE)/Serious Adverse Event (SAE) review.<br>4. Cost data collection and analysis |
| 8 | Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material. | Calculated sample size: 2000 participants No. of participants in the interventional arm receiving study product: 1000 No. of kits to be imported (with 10% wastage): 1100 |
| 9 | Site of the trial | Clinical Trial Unit, Aga Khan University Hospital Main Campus, Stadium Road, Karachi. |
| 10 | Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members. | Attached. |
| 11 | Approval of National Bio-ethics Committee (NBC) | Attached.<br>Ref:No.4-87/NBC-667/21, dated 17th August 2021. |
| 12 | CV's of the Investigators | CVs of following (P.Is) are attached:<br>i. Dr. Saeed Hamid (PI), Director CTU, Professor & Consultant Gastroenterologist, Department of Medicine, Aga Khan University Hospital, Karachi.<br>ii. Dr. Aliya Hasnain (Co-PI), AKUH, Karachi. |
| 13 | GMP certificate along with COPP & free sale certificate of the investigational product. | Not provided & claimed as N/A. |
| 14 | Pre-clinical/clinical safety studies | Instead of any published data applicant provided FDA Summary of Safety & Effectiveness Data (PMA P080027) & WHO prequalification public report of invitro diagnostic devices. |
| 15 | Summary of Protocol | Attached. |
| 16 | Summary of Investigator Brochure | Instead of Investigator's Brochure device (user manual) is attached. Investigator's Brochure as per ICH-GCP guidelines need to be provided. |
| 17 | Adverse Event Reporting Form | Not provided.<br><br>Claimed that, the study is of low-risk HCV STs which have already been approved for patient use, the probability of an AE or SAE occurring to a |

| | | |
|---|---|---|
| | | study participant to be associated with the investigational products is extremely low. Nevertheless, safety and incident reporting are described in Section 7 Safety and Incident Reporting of protocol, but no adverse event reporting form is provided. |
| 18 | No of patients to be enrolled in each center. | For Pakistan:<br>2000 Subjects |
| 19 | Name of Monitors & Clinical Research Associate | Dr. Erum Choudhry, Senior Clinical Research Associate, M/s Metrics Research, Karachi.<br>Dr. Areeba Waqas, Lead Clinical Operations & Medical Affairs, M/s Metrics Research, Karachi. |
| 20 | Evidence of registration in country of origin. | Claimed that, the OraSure test is registered with the FDA, USA but only pre-market approval "FDA Summary of Safety & effectiveness Data" is attached.<br>No evidence for registration/approval is provided. |
| 21 | Copy of registration letter (if registered in Pakistan) | N/A. |
| 22 | Sample of label of the investigational product / drug. | Device user manual is provided. |
| 22 | Duration of trial | 08 Months |
| 23 | Undertaking on Stamp paper | Attached. |

04. After initial scrutiny following shortcomings observed:

i. No evidence for registration/approval in country of origin is provided.
ii. Adverse Event Reporting Form is not provided.
iii. OraSure testing kit/device (user manual) is attached. Investigator's Brochure as per ICH-GCP guidelines need to be provided.
iv. GMP certificate along with COPP & free sale certificate of the investigational product is not provided.
v. Phase of trial/study is not described.
vi. Attached protocol is a draft not signed by Sponsor/PI.
vii. Details regarding financing & insurance is not described in the protocol.
viii. **Memon Goth Hospital is mentioned as nearby site** for testing. The mentioned site is not approved by DRAP as clinical trial site.

05. Accordingly, shortcomings communicated to the applicant dated 06th October 2021 & applicant submitted reply on 09th October 2021. The reply is as follows:

| S.No. | Shortcomings | Reply |
|---|---|---|
| 01 | No evidence for registration/approval in country of origin is provided. | The OraSure test is registered in the US and FDA approved. We are testing a self-test version which if successful can be used in Prime Minister's Hepatitis C Elimination campaigns to have more people tested. The WHO has already |

| | | |
|---|---|---|
| | | recommended this test for use and the guideline will be coming out soon.<br>• FDA approval<br>• WHO Prequalification Report |
| 02 | Adverse Event Reporting Form is not provided. | Adverse events are expected to be minimal. This test only involves taking a sample of saliva from the mouth and sending it for testing. In any case of an adverse event, we will record the event as it happens and report it. In the extremely rare event, and SAE happens (God forbid), this will be reported using the CIOMS Form |
| 03 | OraSure testing kit/device (user manual) is attached. Investigator's Brochure as per ICH-GCP guidelines need to be provided. | Investigator Brochures are meant only for drug trials, not for device trials. For these, a User Manual is required. |
| 04 | GMP certificate along with COPP & free sale certificate of the investigational product is not provided. | GMP, COPP and Free Sale Certificates are requirements for drug trials, not device trial. Further, manufacturing compliance is also provided in FDA approval.<br>• FDA approval |
| 05 | Phase of trial/study is not described. | This is a Phase 3 trial as it compares HCV self-testing to standard testing. |
| 06 | Attached protocol is a draft not signed by Sponsor/PI. | Signed protocol attached |
| 07 | Details regarding financing & insurance is not described in the protocol. | The trial is financed by FIND (Foundation for Innovation in Diagnostics), which is a WHO supported organization.<br>Insurance for the study from local insurance agency is attached. |
| 08 | **Memon Goth Hospital is mentioned as nearby site** for testing. The mentioned site is not approved by DRAP as clinical trial site. | Patients will be referred to Memon Goth Hospital for routine testing of HCV, and this is not a part of the study. Only compliance to getting the test done will be looked at. Memon Goth Hospital is a Sindh Govt facility where testing for HCV antibody is done. It is not a test site for purposes of this study. |

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

7. Dr. Saeed Hamid, Director CTU Aga Khan University Hospital, Karachi joined the meeting online through Zoom & briefed the Committee regarding the case & answered the questions raised by the CSC members.

**Decision:**

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

**AGENDA ITEM XXIX:**

**TRA-1129940, LONGITUDINAL 2-YEAR BONE MARROW STUDY OF ELTROMBOPAG OLAMINE (SB-497115-GR) IN PREVIOUSLY TREATED ADULTS, WITH CHRONIC IMMUNE IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP).**

Mr. Yasir Iqbal a subject of clinical trial titled ***"TRA-1129940, Longitudinal 2-Year Bone Marrow Study of Eltrombopag Olamine (SB-497115-GR) in Previously Treated Adults, with Chronic Immune Idiopathic Thrombocytopenic Purpura (ITP)"*** submitted the following complaint in the office of Director, Division of Pharmacy Services:

"*In his complaint he informed that on 13th March, 2010, he became ill and went to Hameed Latif Hospital for a check-up from Dr. Zeba Aziz. He was admitted in the hospital and stayed at the hospital for 10-12 days and was informed that he had Chronic Immune thrombocytopenia (ITP). Accordingly, his treatment was started and he had to visit the hospital 2-3 times a week. But, three months after the start of treatment, Dr Zeba Aziz informed him about a medicine namely Eltrombopag and said it was very successful in other countries. He said that he was made assured that he would be cured with the treatment of that medicine. It was also informed as that medicine was under clinical trial at that time in Pakistan, so it will be provided free of cost to him and the sponsored company would bear his expenses and if any mishap happened, the company would be responsible. He was also assured that the company is a multinational, namely GSK. He blamed Dr. Zeba Aziz, Dr. Muhammad Akram and Dr Abbas for their greediness for the fund of the trial because he was compelled to participate in the trial as he was their regular patient; therefore, he was given code number 000429 in the trial for patient identification. Accordingly, he informed that the treatment was started with 25mg of Eltrombopag. In the second week, the dose was increased to 50mg due to which he said that he felt pain and inflammation in his leg and went to the hospital for a check-up, where Dr. Zeba Aziz prescribed pain medication and increased the dose to 75mg. He said after taking 75mg Eltrombopag, his condition was worsened as he had severe pain and inflammation in leg along with vomiting. He called Dr Abbas and Dr. Zeba and was advised to visit the emergency of Hameed Latif hospital, where his ultrasound, CT scan were performed and was ultimately admitted in ICU. He said that his family was requested to pray for him, as Doctors informed his family that because of Eltrombopag he had developed Deep Vein Thrombosis (DVT) and also to pray that clotted blood should not block his trachea or heart as it would be fatal for him. He was admitted in his hospital and was shifted to warfarin to avoid clotting. He said that clots developed regularly so Dr. Zeba advised him to visit Dr. Ali in Shaukat Khanum Hospital, where after investigation he was asked to install Inferior Vena Cava (IVC) filter, which he did. He said that not only he developed DVT in his leg but also has regular vomiting and cannot eat anything. He further added that his IVC filter is closed now and Doctors have informed him that there would be a big risk in its removal, might be a risk of his life.*

*Concluding the statement, he said that because of commission/ funding, the Doctors of Hameed Latif had made him a guinea pig for the testing of Eltrombopag by not considering the harmful effects of the drug. He said his life has changed as he cannot lift any weight, neither can he go upstairs because of shortness of breath. He also added that he had a running business in Kuwait before the start of that drug, but, he spent his entire asset on his treatment. He requested for help. He also said that the trial of that company should never have been allowed at that time in Pakistan as in 2007 and 2008, GSK was fined for 300 Billion Dollars by US Court due to death of 14 children in a trial with a drug of that company. Further, in China, that company was also fined for 490 million pounds because of giving money to Doctors. Therefore, it would have been good, if that company had never been allowed for that trial in Pakistan. In the end, he said the doctors have ruined his life and future because he could not lift his children nor can he walk and earn for them. Therefore, he said that he needs justice to be done in the matter.*

2. Among a list of documents, he provided, there was a certificate dated 9th January, 2013 of Dr. Muhammad Akram, Consultant Oncologist, Hameed Latif Hospital, which stated as under:

> *"Mr. Yasir Iqbal, 25 years/Male, resident of Gujranwala, diagnosed with chronic ITP in January, 2010. He then went to Hameed Latif Hospital for his treatment in June, 2010 and was started on to Eltrombopag in August 2010. After 1 month of initiation of Eltrombopag, he developed pain and swelling in left leg. Colour Doppler of the left leg showed extensive Deep Vein Thrombosis (DVT). He was started by Clexane and he responded well to the therapy and thrombosis was recanalized. But, after 3-4 months he again developed DVT leading to pulmonary embolism. When investigated he is also found to have positive for lupus antibody. To avoid this incidence of pulmonary embolism again, an Inferior Vena Cava filter was placed.*
>
> *Now he has been on steroid and immunomodulator drugs for the treatment of his chronic ITP and he is on regular follow up with us."*

3. Accordingly, Director, Division of Pharmacy Services, Chairman, Clinical Study Committee through letters communicated with the following:

a) Punjab Healthcare Commission for investigation and legal action;
b) Pakistan Medical and Dental Council (PMDC) for investigation and initiation of legal action against the concerned doctors;
c) Hameed Latif Hospital for investigation;
d) Provincial Pharmacovigilance Centre, the Punjab for investigation; and
e) GSK Pakistan for explaining their position and submission of the final report of the study.

4. No reply was received from PMDC and the Provincial Pharmacovigilance Centre of Punjab. However, the other three submitted as under:

I. The GSK Pakistan submitted that the subject matter with the complainant, Yasir Iqbal, is sub-judice in Consumer Court of Lahore and since the past few hearings the complainant hasn't been appearing before the concerned judge, despite several opportunities. Alongside, a civil suit was filed against the complainant in Civil Court Lahore, where an injunction order is passed against the complainant and is in a field whereby, the complainant is restrained from maligning the company, making derogatory comments or filing any frivolous complaints during the pendency of his complaint before Consumer Court Lahore. It was said that the complainant has undoubtedly violated the Court Order and the company reserves the right to initiate contempt of court proceedings against him.

II. The Punjab Healthcare Commission replied that the incident took place in the year 2010. However, the Punjab Healthcare Commission Act, 2010 (PHC Act, 2010) was promulgated on 2nd of August, 2010 while Punjab Healthcare Commission was constituted in the year 2011 under the provision of Section 3 of the said Act; therefore, the PCH Act, 2010 does not have retrospective applicability as there is no section/clause in the said Act to that effect. Furthermore, it was said that as per sub-section (7) of Section 4 of the PHC Act, 2010, the commission inter-alia entertains complaints on reference by Superior Courts of the Country i.e. the Honorable Supreme Court of Pakistan and the Honorable Lahore High Court or Government/ Provincial Assembly of the Punjab. Therefore, because of the aforementioned sub-section (7) of

Section 4 of the PHC Act, 2010, the Commission does not have the mandate to probe the instant complaint while remaining within the four corners of Law.

III. Hameed Latif Hospital, Lahore in its reply said that nevertheless, the matter is sub-judice, yet they consider it appropriate to reply to the DRAP and denied each and every averment, allegation, claim statement and demand made by the complainant.

a. It was said the Yasir Iqbal himself approached Dr. Zeba Aziz and her team in March, 2010 for his treatment of ITP. As per standard protocols of treatment of ITP, he was started with treatment of steroids as a first-line treatment for ITP, which did not show any results. Accordingly, he was started on Cyclosporine to increase "the platelet count" as per international acceptable recommendation. ITP did not respond positively to both of these drugs.

b. Professor Dr. Zeba Aziz accordingly recommended alternative treatments options such as Rituximab and/or Intravenous Immunoglobulin IVIG, however, Yasir Iqbal refused to receive this treatment on account of cost and expensiveness. Dr. Zeba Aziz also recommended "Splenectomy" a surgical procedure, that Mr. Yasir also refused to cite the lack of funds and requested to doctors of the hospital for financial assistance. Due to this continuous refusal of Mr. Yasir of the alternative standard expensive treatment available in Pakistan, the treatment of administering "Eltrombopag" for Chronic ITP was proposed by Dr. Zeba Aziz as free of cost under clinical trial. Therefore, Dr. Zeba proceeded with international protocols of treatment of ITP and only enrolled the subject in the study when Mr. Yasir refused to went for other treatment options. He was informed about possible side effects in both verbal and written consent forms.

c. The treatment was started on 12$^{th}$ of August, 2010 with the standard dose of 50mg as per protocols and was he asked to visit on weekly basis for monitoring and progress. It was submitted by the hospital that Mr. Yasir was never given Eltrombopag 25mg which he falsely mentioned in his complaint showing his mala fide intentions. His platelets did not increase with 50mg of Eltrombopag, therefore, as per the protocol of the study, the dose was increased by 25 mg after two weeks to 75mg once daily on 6$^{th}$ September, 2010.

d. On 5$^{th}$ day of the new dose treatment, the subject informed the doctors on 11$^{th}$ September, 2010 that he had pain in his leg. The investigational drug was stopped immediately as Doppler ultrasound showed Deep Vein Thrombosis (DVT). He recovered from this acute condition in the next five days and all the cost was borne by the Sponsor i.e. GSK for this treatment.

e. The twelve other subjects did suffer any side effects and their treatment was successful. He was provided with injection Clexane free of cost by the trial team for 6 months that resolved his DVT completely in February, 2011 as Doppler showed no evidence of any thrombus in his leg veins. He was advised to change his lifestyle like exercise and reduction of weight and control his blood pressure to minimize the reappearance of clots in his body. His last visit to Hospital was in July, 2013.

f. According to reviewed records he recovered completely from his SAE of "thromboembolic event", unfortunately, he developed DVT again after about 2 months, this time he was not on Eltrombopag for 6 months. The recurrent DVT was attributed by Doctors to his obesity, lazy lifestyle, smoking history and chronic ITP.

g. It was said that Yasir Iqbal went to the Court with the statement that the Eltrombopag was wrongly prescribed to him and has now changed his stance from wrong medicine to wrong dose prescription, although both of his stances are baseless. The matter is sub-judice in the court, yet out of respect for the DRAP, they have submitted the reply.

5. Meanwhile, the complainant approached the Lahore court and filed a writ petition under Article 199 of the Constitution of the Islamic Republic of Pakistan in case W.P. No. 45033 of 2021 titled "Yasir Iqbal Versus Government of Pakistan", where he prayed that Respondent No. 2 i.e. Drug Regulatory Authority of Pakistan may kindly be directed to make arrangements for the petitioner to get treatment in a foreign country and to bear all the expenses of the treatment of the petitioner in foreign country expeditiously accordance with the law, to meet the end of justice. The Honorable court on 09th of July, 2021 ordered as under:

*"**Through instant petition, petition is seeking direction for decision on his pending application for making arrangements for petitioner to get treatment in foreign country and also compensate him for his treatment. Add that petitioner would be satisfied if a direction is issued to respondent No. 2 to decide the petitioner pending application strictly in accordance with law, after hearing petitioner and all concerned, through a well-reasoned speaking order, preferably within a period of fifteen days from the date of receipt of certified copy of this order."***

6. In compliance with the decision of Honorable court the case was placed before CSC in its 29th meeting held on 05th August 2021. CSC decided as follows:

***Decision of 29th CSC meeting.***

*CSC after detailed deliberation decided to defer the matter and to call the applicant/ complainant, Dr. Zeba Aziz of M/s Hameed Latif Hospital, Lahore and representative of GSK, Pakistan for personal hearing to have their point of view on the issue in forthcoming CSC meeting to proceed further.*

7. Accordingly, the letters have been sent through WhatsApp & email on 24th August 2021.

8. List of respondents is as follows:

i. Mr. Yasir Iqbal S/o Zafar Iqbal (the petitioner/complainant/trial subject). Resident near Bismillah CNG & Bismillah Marriage Hall, GT Road, Muridke, District Sheikhu Pura.
ii. Dr. Yousaf Hasan Khan, Country Medical Director, **Glaxo Smith Kline**, Pakistan Ltd. 35-Dockyard Road West Wharf, Karachi.
iii. Dr. Irfan Ishaq, Additional Medical Director, M/s **Hamid Latif Hospital**, 14-Abu Bakr Block, New Garden Town, Lahore.
iv. Dr. Zeba Aziz, M/s **Hamid Latif Hospital**, 14-Abu Bakr Block, New Garden Town, Lahore.
v. Dr. Muhammad Akram, M/s Hamid Latif Hospital, 14-Abu Bakr Block, New Garden Town, Lahore.
vi. Dr. Abbas, M/s Hamid Latif Hospital, 14-Abu Bakr Block, New Garden Town, Lahore.

9. The complainant and Respondents have been also contacted telephonically for appearance/personal hearing before CSC in its 31st meeting.

10. The case was placed before 31st CSC meeting held on 26th August 2021. Discussion & decision of the Committee is as follows:

11. Discussion & presentation:

Secretary CSC past AD(IV) to present the case AD PS(IV) presented the case before the CSC and informed that trail titled "**,** LONGITUDINAL 2-YEAR BONE MARROW STUDY OF ELTROMBOPAG OLAMINE (SB-497115-GR) IN PREVIOUSLY TREATED ADULTS, WITH CHRONIC IMMUNE IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)", which was approved by Ministry of Health in 2010 and was approved we conducted at following sites

1) National Institute of Blood Diseases Karachi.
2) Hameed Latif Hospital Lahore.

During the Trial one of the participant Mr M Yasir Iqbal submitted a complaint that in 2010 he was getting treatment from Hamid Latif Hospital for Chronic Immune thrombocytopenia and meanwhile during treatment Dr Zeba Aziz (PI) of Hameed Lateef Hospital informed the patient about drug and trial and started therapy with 25mg and next with 20mg and after 2 weeks with 75mg later on subject completed a based development of severe pain inflammation & vomiting in left legs he called Dr Zeba Aziz Dr Zeba Asked him to admit in the ICU later on it was informed that he has developed deep vein thrombosis he was started the warfarin treatment later on installed inferior vena cava filter now he has complained that his filler has been choked he is not fending any treatment blaming that hospital has not informed about this trial he also written application that this trial has been fined in US , China later on he went to the high court & High court decided the case & ordered as follow:

*"**Through instant petition, petition is seeking direction for decision on his pending application for making arrangements for petitioner to get treatment in foreign country and also compensate him for his treatment. Add that petitioner would be satisfied if a direction is issued to respondent No. 2 to decide the petitioner pending application strictly in accordance with law, after hearing petitioner and all concerned, through a well-reasoned speaking order, preferably within a period of fifteen days from the date of receipt of certified copy of this order."***

Copy of order received by the division. Chairman CSC invited the complainant Mr. M. Yasir Iqbal for personal hearing & presentation of his point of view before CSC. M.Yasir Iqbal joined the meeting in person & informed the Committee that in March-2010 he was ill so he went to Hamid Latif Hospital Lahore from Gujranwala. Someone informed him to go to Hamid Latif Hospital Lahore for check-up because his platelets were at 15 percent (15000). At Hamid Latif Hospital, Dr. Zeba Aziz treated & admitted him in the hospital. He was hospitalized for 10-15 days, where he was treated. After discharge from the hospital, he was called 2-3 times a week with CBC report & also started Deltacortil and after 2-3 months, Dr. Zeba Aziz (PI) briefed regarding M/s GSK & its clinical trial & satisfied him regarding trial drug & the trial. It was also informed that during trial complete treatment will be given in case of any Serious Adverse Event. Inform Consent Form also shared. Afterwards trial started with 25mg of IMPs & after 2-3 days he complained regarding inflammation in left leg but the PI increased the dose up to 50mg. Besides to stop trial medication & care of adverse event, Dr. Zeba Aziz (PI) increased the dose up to 75mg. Mr. Yasir claimed that PI should not recruit him in the trial as at that time his platelets level was sufficient. He also claimed that the M/s GSK renowned all over the world for bribing doctors & in 10 countries they are fined. Due to Deep Vein Thrombosis (DVT) he went to all renowned specialists of Lahore including Dr. Javed Akram. At present IVC filter which was installed on advice of Dr. Zeba Aziz from Shaukat Khanum Hospital by Dr Ali Raza. IVC filter choked in 2015 then he went to Dr Zeba Aziz where a representative Doctor From M/s GSK was also available, after seeing reports they said that the reports are clear. But after 2015 IVC filter was choked and IVC vein is blocked. He got test from Al Noor Hospital, CMH, Shifa Hospital and visited to different surgeons for his health recovery. Due to illness he

unable to perform normal functions even he barely can walk. Mr Yasir informed he had a business of tyre in Kuwait, statement of also be reproduced and due to trial and subsequent ADRs/ SAEs his business destroyed and he is now unable to do anything, he also informed that he was a married person and have three children's and unable to do for then. All the doctors he met said that there is no cure / treatment in Pakistan.

Dr Javed Akram said that our all sympathise are with Mr Yasir and informed that he chaired the disciplinary committee of PMDC for 10 years and also worked with health care commission and his opinion is that this forum have not any authority to proceed against any manufacturer on any medical specialist/ researcher and the study not approved by CSC. He further added that the proper forum for the case is Punjab Health Care Commission (PHCC) are Pakistan Medical Commission (PMC) because there is a proper infrastructure and proper follow up. He wonders that under which clause/ authority, the CSC is deal with this case and its hearing.

Chairman CSC appraised the members that there are directions form honourable Lahore high court and decision of the case within 15 days.

Dr Javed Akram added that we may write to High Court that DRAP has no power to help out in this case because CSC/DRAP can't proceed against any Dr and Hospital so if this forum can't proceed/ help out the complainant so why this forum is dealing with. We can only write the High Court in our drug law and per law we haven't authority proper forum was the case is PMC/PHCC. He further added that the CSC may use my name in reply as I was chaired disciplinary committee of PMDC

Chairman CSC informed the member that the personal hearing is given on direction of Lahore High Court and we are following court directions and that this trial was approved by Ministry of Health and files / records is present, and it is right that we can't proceed against Doctor and Hospital so the case may be forwarded to PMC and same report may be forwarded to the High Court.

Saeed Anjum Khokhar (Advocate M/s GSK Pakistan Ltd.) joint the meeting virtually and informed the members that the complainant had already filed the case at Lahore Consumer Court case and it is pending/sub-judice, another case files by the complainant is in civil court Lahore which is also pending. He further submitted that while hearing the said petition no notice is served by the Court and they have no idea regarding its content of petition. So, they are not in a position to appraise it. He also supported Dr Javed Akram's opinion regarding jurisdiction under the DRAP Act. He clarified that the direction passed by the High Court can't give/authorise jurisdiction to any organization. He further informed that in the first hearing of the petition the complainant requested to High Court that his application is pending so decide the application and, in the court, order it is clearly mention that "this learned authority is legally bond the decide the application strictly accordance with law" after hearing petition & all concerned through well-reasoned, and law is that DRAP has no jurisdiction in such cases. He further submitted that complainant had concealed the facts about his cases in consumer and civil court Lahore. The complainant should inform all facts in this hearing.

Mr Arslan Nadir (Advocate of Dr Zeba Aziz, Dr Abas Khokhar and Dr Akram of Hamid Latif Hospital Lahore) joint the meeting virtually and apprised the CSC about health care commission that complainant had already exhausted two forums (i.e. Consumer Court and Civil Court) and exhausted the third forum (i.e. Health Care Commission) vide complaint no 230 / 2021 (reference No of complaint in PHCC regarding negligence). All details are concealed here in the hearing by Lahore by the complainant. He further added that refer to writ petition no 45003/2021 there are 14 paras in the petition but complainant does not describe any details regarding civil court /consumer court and PHCC and after concealment of the facts on application is forwarded to this forum. Proper forum is consumer court where Mr Yasir filed in complaint 2015 which is still pending and its next hearing on 5th /7th September 2021, another forum used by the complainant his health care commission where detail reply his already filled and health care commission is right forum for the case as health care commission fined out the problem faced by the complainant is either from M/s GSK product or other aspects or involved. He further added that as the complainant concealed the facts it is difficult to sort out the matter on a zoom meeting and is unfair. DRAP has no jurisdiction to entertained this application thirdly consumer court is special law and special law prevails general laws fourthly PHCC

is special law and after enactment if complainant has any complainant any hospital or negligence of Dr Zeba Aziz Dr Abbas Khokhar and Dr Akram's professional skills and complainant already exhausted the forum.so coming to the DRAP to just harass/blackmail as discussed matter may forwarded to PMC so it is suggested to ask from complainant at which forum he want to solve the matter as the same matter at 5 different forum is not the way to deal the case. Complainant already filed the case at consumer court and civil court and due to evidence submitted by the complainant and after submission of evidence production will cross the evidence after cross checking of evidences submitted by the complainant and respondents then any forum decides the case.
Chairman CSC asked the complainant regarding cases in consumer and civil court. Mr Yasir replied that it is to that he filed the cases in civil and consumer courts but these forums can't deal with manufacturer M/s GSK, so who will ask the manufacturer. he added that DRAP approved the medicines of M/s GSK so why not DRAP may ask from GSK about trial subject record.
Secretary CSC submitted that the case was also discussed in 29th CSC meeting and decided as follow:

*CSC after detailed deliberation decided to defer the matter and to call the applicant/ complainant, Dr. Zeba Aziz of M/s Hameed Latif Hospital, Lahore and representative of GSK, Pakistan for personal hearing to have their point of view on the issue in forthcoming CSC meeting to proceed further.*

Accordingly, letters were issued and also requested that if respondents intend make any submission, same may be furnished within 7 days positively along with mobile & landline numbers, time & date will be communicated later on and letters written on 6th august 2021. So, we should have some written argument or material this division to prepare the case in accordance with the law and submission of respondents.
Chairman CSC further added that biostudy rule 2018 any complaint regarding trials may be discussed by the CSC and even can be forward for persecution
Advocate M/s GSK replied that, they want to submit detail reply so the copy of writ petition and application may be supplied so they will submit their reply with evidence.
Chairman CSC asked the members to submit their opinion and informed that high court ordered to conclude the matter within 15 days and there is provision in the rules to decide any complaint. So, it may be decided as suggested by Dr Javed Akarma that court may be informed that as ordered the personal hearing was given to complainant and respondent and it is infirmed that the proper forum the case is Pakistan Medical Council (PMC) and Punjab Health Care Commission (PHCC) so it may be requested to High Court that direction may be passed to PHCC and PMC. Secondly it may be decided to refer the case to PMC to heir the complaint as per their rules and decide the case and the same may be informed to the court that the Committee referred to matter to PMC.
Dr Javed Akram again apprised that the case is beyond the jurisdiction of this forum and as the court referred the case to CSC so the court may be guided that the case may be referred to the appropriate forum of jurisdiction. Further it may be informed that the Committee take up the matter as per direction but we have no jurisdictions to take action against any hospital or professional.

Dr. Javed Akram added that the CSC has given hearing to the complainant & CSC also heard the respondents also. Members known about their powers. Mr. Yasir has complaints regarding Doctors, Hospital & Manufacturer and all three respondents can't be proceeded under the Bio-Study Rules 2017. Under the Drug Law manufacturer can't can be dealt but it is an imported drug & GSK Pakistan not manufacture it in Pakistan and a generic also available in market & the drug used in thrombocytopenia.
If an ADR in a study is observed it should be established that weather it is due to product or disease related. So, it is suggested that CSC has given opportunity to complainant of hearing as per orders of the Lahore High Court and given ample chance.
As per complaint there are thee respondent 1, Hameed Latif Hospital 2, Doctor and Manufacturer and for the case the two authorities have jurisdiction 1) PMC which can only able to proceed against

their license holder (Doctors) and they can't proceed against any nurse or Hospital. Health Care commission can take action against Hospitals, so all the matter may be forwarded to the High court that the Committee take up the matter and discussion may be forwarded that under the drug law it is not in our jurisdictions, under the Drug Act if a company manufacturer sub-standard drug so can be proceeded. It is an FDA approved drug & not manufactured in Pakistan and imported to Pakistan, he informed that he prescribes the drug under reference on daily basis it is not an experimental drug so far and it's a lifesaving drug, if someone gets ADRs we can't proceed against any one. So, it should be written to court that we hear out the case and this is not a proper forum and complainant already filed the case on proper forum PHCC, Civil Court, consumer court so it should not be prolonged and just to write back to the honourable Lahore High court that this case is not in our jurisdictions.
Dr Farhana Badar and Dr Rizwana Chaudhary agreed with Dr. Javed Akram point of view. Dr Rizwana added further that at this forum we can't decide these types of matters, even if it a trial related patient, he has given consent for that trial. so, this type of cases should be discouraged at this forum.
Chairman CSC concluded the case that we should submit the high court that CSC the matter and the relevant forum is PHCC and PMC so may be forwarded to appropriate forum.

**12. 31st CSC Meeting Decision:**

*The CSC after deliberation and detailed discussion decided to request the honorable Lahore High Court that, in this case the appropriate forum for redressal of grievances of the complaint is Punjab Health Care Commission (PHCC) or Pakistan Medical Commission (PMC).*

13. Before issuance of decision the matter was forward to Division of Legal Affairs-DRAP for consultation & corrections. Division of Legal Affairs-DRAP replied as follows:

> *Reference to the report placed on file (F/A) and copy of the petition (F/B) the Division of Pharmacy Services vide Letter No. F. 3-3/2010-ADC (CT) Vol-III dated 04.05.2020 and 21.06.2020 has already declared its jurisdiction on the matter, the ibid letters were placed before the Honourable Judge LHC in W.P No. 45033/2021, therefore, the Honourable court referred the matter to the DRAP for appropriate order. It is, therefore, requested to consider arguments of both the complainant and the firm and pass a speaking order on merit. Final order of the Committee on issue shall be communicated to the honorable court. 111. Submitted please.*

14. Written reply received from M/s GSK Pakistan Limited, Karachi & M/s Hamid Latif Hospital, Lahore also attached **(Annex-XII)**. It was discussed & decide to place the matter again before CSC.

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

***NOTE:*** *The minutes/report of the court case will be prepared afterwards & shared accordingly as per discussion/advice of the Chairman CSC.*

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**AGENDA ITEM XXX:**

**ICU MEDICAL VENTILATOR ALNOVENT AVB-100 DEVELOPED BY ALSONS.**

This is case of Ventilator manufactured by M/s Alsons for PMVS Alnovent AVB-100. The application on Form-II has been submitted by Dr. Hina Nabi Ahmed, Assistant Professor, AIMC, lahore wherein the applicant has submitted requisite Fee, Preclinical studies conducted by Pakistan

engineering council and NBC approval for amended protocol version 1.2 while Protocol version 1.2 not submitted. The IRB approval is also required for amended protocol.

2. **Submitted for consideration of CSC**

**Decision:**

*The CSC after deliberation / detailed discussion decided to recommend the clinical validation application of ICU Medical Ventilator Alnovent AVB-100 Developed by Alsons as per three newly approved TORs & proforma for evaluation & inspection of clinical validation of ventilator trial applications and furnish the results / reports in the sequence as approved by the Committee.*