MINUTES OF THE 43RD CLINICAL STUDIES COMMITTEE MEETING (SUMMARY)

Pharmacy Services Division, Drug Regulatory Authority of Pakistan
File No: 16-43/2023-CSC (PS)

JUNE 02, 2023
DRUG REGULATORY AUTHORITY OF PAKISTAN
Prime Minister's National Health Complex, Park Road, Chak Shahzad, Islamabad.

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The 43rd meeting of the Clinical Studies Committee was held on 02nd June, 2023 in the Committee room, Drug Regulatory Authority of Pakistan, G-9/4, Islamabad. The meeting was chaired by Dr. Obaidullah, Director Pharmacy Services. The meeting was started with recitation of the Holy Verses.

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

Sr. No.	Name	Designation	
i.	**Dr. Obaidullah**	Director Pharmacy Services Division.	*Ex-officio Chairman*
ii.	**Prof. Dr. Fazal Subhan**	Department of Pharmacy, CECOS University of IT & Emerging Sciences, Peshawar, Khyber Pakhtunkhwa.	Member
iii.	**Dr. Faiza Bashir**	Nominee of Chairman, Pakistan Health Research Council, Islamabad.	Member
iv.	**Dr. Mirza Tasawer Baig**	Associate Professor in the Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi & Clinical Pharmacist at Dr. Ziauddin Hospital, Karachi, Sindh.	Member
v.	**Ahsan Ul Haq Athar**	Deputy Director, Pharmacy Services Division.	*Ex-officio Secretary*

3. Following members attended the meeting online through Zoom:

i.	**Prof. Munawar Alam Ansari.**	Professor of Pharmacology, Dean Faculty of Pharmacy, Liaquat University of Medical Sciences, Jamshoro, Sindh**.**	Member
ii.	**Prof. Dr. Saeed Ahmad Khan**	Professor of Medicine Bolan Medical College Quetta presently serving as head of Medicine Department Jhalawan Medical College Khuzdar, Balochistan.	Member
iii.	**Mr. Waqas Latif**	Data Analyst/Biostatistician in Quality Enhancement Cell (QEC) at University of Health Sciences, Lahore, Punjab.	Member

4. Mr. Nouman Yousuf, Hafiz Muhammad Jawad Ali, Malik Muhammad Asad and Shafqat Hussain Danish assisted the Committee and Secretary in presentation of the agenda.

AGENDA ITEM I:

SERIOUS ADVERSE EVENTS REPORTED FOR CLINICAL TRIAL TITLED, "A MULTI-CENTER, RANDOMIZED, BLINDED, PLACEBO-CONTROLLED, PHASE-III CLINICAL STUDY TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF SARS-COV-2 BIVALENT mRNA VACCINE (LVRNA021) AS BOOSTER IN PARTICIPANTS AGED 18 YEARS AND OLDER WHO COMPLETED PRIMARY/1 BOOSTER DOSE(S) OF SARS-COV-2 VACCINATION" F.No.03-35/2023-CT (PS)

Decision:

The CSC after detailed discussion and deliberation decided:

i. *That the Study/Clinical Trial titled "A Multi-Center, Randomized, Blinded, Placebo-Controlled, Phase-III Clinical Study to Evaluate the Efficacy, Safety and Immunogenicity of SARS-COV-2 Bivalent mRNA Vaccine (LVRNA021) as Booster in Participants aged 18 Years and Older Who Completed Primary/1 Booster Dose(s) of SARS-COV-2 Vaccination" will remain suspended for further enrolment.*

ii. *To direct the National PI/PIs and the CRO for compliance of following points:*

   a. *To complete laboratory testing on study participants. The SAEs and laboratory test reports will be placed before respective IRBs and DSMB. All minutes / reports of aforementioned forums related to instant trial will be shared with Pharmacy Services Division, DRAP for further evaluation and onward submission to CSC in its forthcoming meeting.*
   b. *To strictly comply following directions already communicated vide letter No. 16-42/2023-CSC-PS dated 19-05-2023 in the best interest of study volunteers/subjects:*
      i. *Remain in close contact with all trial participants/subjects*
      ii. *Take all necessary measures/actions to ensure the safety of the participants/subjects*
      iii. *Provide necessary medical treatment, if required.*
   c. *CRO will ensure that all cases of medical insurance and compensation for family of deceased have been processed and status will be shared for consideration of CSC in forthcoming meeting.*

iii. *Advised Pharmacy Services Division to coordinate with the NBC for joint meeting to discuss/ deliberate on observations / recommendations of the panel and to devise the way forward for ethical and regulatory compliances.*

AGENDA ITEM II:

AN INTERNATIONAL, RANDOMIZED, BLIND, ACTIVE CONTROLLED PHASE I/II/III STUDY TO INVESTIGATE THE SAFETY AND IMMUNOGENICITY OF BIVALENT MRNA VACCINE (RBMRNA-909) AS A BOOSTER DOSE IN COVID-19 VACCINE EXPERIENCED HEALTHY ADULTS. F.NO.03-41/2023-DD-CT-I(PS)

Decision:

The CSC discussed the request for withdrawal of the application and request was acceded.

AGENDA ITEM III:

APPLICATION FOR APPROVAL OF PATIENT RECRUITMENT FLYER-POSTER FOR CLINICAL TRIAL TITLED AS "A PHASE 3 RANDOMIZED, DOUBLE BLIND, PLACEBO-CONTROLLED STUDY TO EVAUATE THE EFFICACY AND SAFETY OF BEMNIFOSBUVIR IN HIGH RISK OUTPATIENTS WITH COVID-19. F.NO.03-37/2023-CT(PS)

Decision:

The CSC after detailed deliberation decided to delegate its powers to Chairman CSC for decision of subject trial's Recruitment Flyer-Poster after NBC approval.

AGENDA ITEM IV:

APPLICATION FOR APPROVAL OF PROTOCOL AMENDMENT FOR CLINICAL TRIAL "PERI-OPERATIVE ISCHEMIC EVALUATION-3 (POISE-3) TRIAL. F.NO.03-07/2019-CT(PS)

Decision:

The CSC after discussion decided to defer the case and directed the applicant/PI to submit IRB, NBC and DRAP's approvals for Protocol version 5.0, 6.0 & 7.0 along with prescribed fee(s) and all prerequisites as per the Bio-Study Rules, 2017 & Guidance on Clinical Trials Application (Guidelines).

AGENDA ITEM V:

APPLICATION FOR APPROVAL OF PROTOCOL AMENDMENT FOR CLINICAL TRIAL "A RANDOMIZED PHASE III PLACEBO-CONTROLLED TRIAL OF COLCHICINE FOR THE PREVENTION OF PERI-OPERATIVE ATRIAL FIBRILLATION (COP-AF). F.NO.03-37/2020-CT(PS).

Decision:

The CSC after discussion decided to defer the case and directed the applicant/PI to submit IRB, NBC and DRAP approvals for Protocol version 4.0 & 5.0 along with prescribed fee(s) and all prerequisites as per the Bio-Study Rules, 2017 and Guidance on Clinical Trials Application (Guidelines).

AGENDA ITEM VI:

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

Decision:

The CSC considered the recommendations of inspection panel and after deliberations decided as follows:

a. *To approve the renewal of licence (w.e.f. 03rd February 2023 to 02nd February 2026) for Phase-III and IV Clinical Trials only.*
b. *to direct the applicant for submission of complete application for Phase-I and II Clinical Trial Site, situated at Dar-Us-Shifa with all prerequisites as per the Bio-Study Rule, 2017.*

AGENDA ITEM VII:

APPLICATION FOR LICENSE TO ACT AS CLINICAL TRIAL SITE FOR PHASE-II FROM NATIONAL INSTITUTE OF BONE MARROW TRANSPLANT, CMH, RAWALPINDI F. No.15-28/2023-CTS.

Decision:

The CSC after detailed deliberation, discussion and considering the recommendations of inspection panel, deferred the case for fulfillment of following shortcomings and other prerequisites as per the Bio-Study Rules, 2017.

(i) A well-defined layout plan of the facility and re-organization of different sections of CTU as per GCP guidelines.
(ii) Designated subject retaining areas, investigational drug administration area, pharmacy and record room with lock and key (control entry).

AGENDA ITEM VIII:

APPLICATION FOR LICENSE TO ACT AS TRIAL SPECIFIC (PHASE-III) CLINICAL TRIAL SITE FROM DEPARTMENT OF MEDICAL ONCOLOGY, ALLIED HOSPITAL, FAISALABAD F. No.15-29/2023 DD (PS).

Decision:

The CSC after detailed deliberation, discussion and considering the recommendations of inspection panel decided to grant licence to act as Clinical Trial Site for a Phase-III Clinical Trial titled, "A Randomized, Double-Blind Clinical Study of the Efficacy and safety of BCD-201 (JS BIOCAD) and Keytruda in patients with Unresectable or Metastatic Melanoma "and permitted to conduct the said trial.

AGENDA ITEM - IX:

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).

Decision:

The CSC after detailed deliberation, discussion decided to refer back reports to the CRO and PI and directed them to submit the same alongwith input/ report of IRBs and DSMB.

AGENDA ITEM X:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "A MULTI-COUNTRY, MULTI-CENTER, OPEN-LABELLED, RANDOMIZED, CONTROLLED, EXTENDED PHASE III CLINICAL TRIAL TO EVALUATE THE IMMUNOGENICITY AND TOLERABILITY OF SABIN STRAIN INACTIVATED POLIOVIRUS VACCINE ADMINISTERED WITH OR WITHOUT ROUTINE INFANT VACCINES", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-40/2023-CT (PS).

Decision:

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

i. *Approve the Phase-III Clinical Trial titled, "A MULTI-COUNTRY, MULTI-CENTER, OPEN-LABELLED, RANDOMIZED, CONTROLLED, EXTENDED PHASE III CLINICAL TRIAL TO EVALUATE THE IMMUNOGENICITY AND TOLERABILITY OF SABIN STRAIN INACTIVATED POLIOVIRUS VACCINE ADMINISTERED WITH OR WITHOUT ROUTINE INFANT VACCINES" under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site(s):*
   a. *Aga Khan University Hospital, Karachi (CTS-0003)*
   b. *The Central Hospital, Gujranwala. (CTS-0081)*
ii. *Direct the PI to closely monitor trial subjects and maintain follow-up record to ensure the safety of the trial participants and PI will submit trial progress report of 50 initial subjects after endorsement from Data Safety & Monitoring Board/Committee.*
iii. *Approve the following quantities of IMPs to be imported:*

Study Intervention	*Test Drug*
Intervention Name	*Poliomyelitis Vaccine (Vero cells), In Activated, Sabin Strain (sIPV)*
Total Subjects to be recruited in Pakistan	*720*
Dose Formulation	*Prefilled Syringes*
Each Prefilled Syringe Contains	*Poliovirus Antigen; 15DU (type I) 45DU (type II) and 45DU (type III)/0.5ml*
Quantity to be imported	*720x3 (3 doses) = 2160+5% (buffer) = 2268 Prefilled Syringes*
Total boxes to be imported	*227*

iv. *The approval letter for this trial will be issued after submission of revised IRB approval from M/s Aga Khan University Hospital, Karachi.*

AGENDA ITEM XI:

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

Decision:

The CSC after detailed deliberation, discussion decided to defer the case and directed as follows:

i. *Shortcomings of the application will be communicated to the PI for the last time for fulfillment within 30 days, after which the application will be placed before CSC for final decision.*
ii. *Further, all those application, for which the shortcomings/ queries have been communicated and replies from applicant/PI are still pending/ awaited, a final letter will be issued to all applicant to fulfill all deficiencies within 30 days, after which applications will be placed before CSC for decision.*

AGENDA ITEM XII:

APPLICATION FOR THE USE OF GRANULOCYTE COLONY STIMULATING FACTOR (GCSF) TRIAL PROTOCOL RECORD. FROM AGA KHAN UNIVERSITY HOSPITAL, KARACH. F. No.03-71/2021-DD (PS)

Decision:

The CSC after detailed deliberation & discussion decided to defer the case due to following shortcomings:

i. *Prescribed processing fee is not provided with this application. Instead of submission of the prescribed processing fee of Rs. 200,000/- PI attached Product Renewal of registration challan copies.*
ii. *Instead of IB PIL of Filgen is attached, whereas, the drug is not indicated for Biliary Atresia. PI using an approved drug in a trial for new indication without informing the local manufacturer & without consent.*
iii. *Referring to the previous application again in this application in the protocol Filgen is mentioned to be used in Pakistan only.*
    a. *Protocol is not signed by Sponsor/PI*
    b. *Protocol mentioning Part I without any Phase & Part as Phase-II, so Part I may be considered as Phase-I.*
    c. *Financing, Insurance/compensation details are not provided in the protocol as per ICH-GCP guidelines.*
vi. *It is mentioned that, USA, Vietnam & Pakistan will be the participating country but as per US Trial Registry USA is not a part of the trial. Further as per the registry AKUH, Karachi is with status of recruiting (Study is not approved yet)*
vii. *In reply of IMPs justification, it is claimed that, locally registered product Filgen will be utilized in Pakistan. Whereas, as per IND approval & US Trial Registry Nupogen have IND approval for the trial.*
viii. ***Anticipated cost of the project is n**ot provided.*
ix. *Ethical approvals from AKUH, following approvals are attached:*
    a. *AKUH-IRB approval for one year dated 22nd April 2019, is attached. (It is the same approval, which was used for previous application, that was not approved by the CSC)*
    b. *AKUH-IRB Extension for another year granted after submission of trial progress report, dated 15th April, 2020.*
    c. *AKUH-IRB Extension for another year granted after submission of trial progress report, dated 11th April, 2021.*
x. *Ethical approval from NBC are as follows:*
    a. *Approval reference letter No.4-87/NBC-396/19/15, dated 03rd July, 2019, for period of one year. (It is the same approval, which was issued for previous application)*

b. *Amendment approval reference letter No.4-87/NBC-396/Amend/19/1304, dated 13th November 2019, for a period of one year. (It is the amendment approval for the previous application but not submitted to DRAP)*
c. *Extension approval reference letter No.4-87/NBC-396/Y2-Extension/20/728, dated 26th November 2020, for a period of another year. (It is the amendment approval for the previous application but not submitted to DRAP)*
d. *It is observed from US Trial Registry that, trial status in Pakistan is "recruiting" and there is no site mentioned for USA.*

xi. *Pre-Clinical and Clinical studies are not provided & it is claimed that, it is a marketed product, but IND is approved for Biliary Atresia which is not an approved indication of the Drug.*
xii. *Sponsor status is not clear, [Holterman, Ai-Xuan, M.D. (Sponsor is a person instead of firm or manufacturer)]*
xiii. *Summary of IB & Protocol are not provided.*
xiv. *Evidence of registration in country of origin for Nupogen, is not provided & claimed that locally produced drug will be utilized.*
xv. *Sample label also shows that the PI conducted the trial without approval as Manufacturing & Expiry dates are printed on the label.*
xvi. *Undertaking on Stamp paper is not provided.*

2. Further, it is decided to grant a last opportunity to the applicant/PI to submit reply with all pre-requisites within 30 days, after which application will be placed before CSC for final decision.

AGENDA ITEM XIII:

APPLICATION FOR DESTRUCTION/DISPOSAL OF UN-USED/LEFT OVAR/EXPIRED IMPs OF CLINICAL TRIAL TITLED, "A PHASE III, endTB (EVALUATING NEWLY APPROVED DRUGS FOR MULTIDRUG RESISTANT TB)", AT THE INDUS HOSPITAL KARACHI. F. No.03-04/2019-DD (PS)

Decision:

The CSC after detailed deliberation and discussion decided that, the Chairman CSC will constitute a panel for:

i. *Reconciliation, verification and destruction of IMPs in category I.*
ii. *Reconciliation and verification of IMPs for re-export in category IIa.*
iii. *Reconciliation and verification of IMPs, which was imported for end-TB trial and to be used in end-TBQ trial in category IIb.*

2. On submission of reconciliation report by the panel, the Chairman CSC will decide the matter of IMPs and its quantities in category IIa & IIb. The necessary NOC will be obtained by PI/CRO from DRAP field office under the Drugs (Import & Export) Rules, 1976, to re-export the IMPs as per quantities approved by the Chairman CSC.

AGENDA ITEM XIV:

REQUEST FOR REGISTRATION OF CLINICAL STUDY TITLED "ANTI-CORONAVIRUS THERAPIES TO PREVENT PROGRESSION OF COVID-19. F. No.03-57/2021-DD (PS)

Decision:

The CSC after detailed deliberation and discussion decided that:

i. *The Chairman CSC will constitute a panel for reconciliation of all IMPs (from all three sites) at CTU, Aga Khan University Hospital, Karachi & panel will also accompany the destruction process after reconciliation.*
ii. *PI and panel are also directed to submit reconciliation and drug destruction report to the Pharmacy Services Division.*

AGENDA ITEM XV:

APPLICATION FOR DESTRUCTION OF EXPIRED/UNUSED INVESTIGATIONAL MEDICINAL PRODUCTS 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).

Decision:

The CSC after detailed deliberation & discussion accepted the request & excuse from the PI and decided that,

i. *The Chairman CSC will constitute a panel for reconciliation of all IMPs (from all three sites) at CTU, Aga Khan University Hospital, Karachi & panel will also accompany the destruction process after reconciliation.*
ii. *PI and panel are also directed to submit reconciliation & drug destruction report to the Pharmacy Services Division.*
iii. *The Pharmacy Services Division will issue an advisory to all CROs/PIs (where applicable) for proper handling of IMPs including but not limited to import of IMPs in accordance with the relevant regulatory requirements.*

AGENDA ITEM XVI:

WHO-GBT FORMAL BENCHMARKING OF NATIONAL REGULATORY SYSTEM OF PAKISTAN.

Decision:

The CSC appreciated the efforts and input of the CT-Team of Pharmacy Services Division & NBC member during GBT-Audit and encouraged the team for fulfilment of remaining GBT tasks including preparation/revision of existing/new SOPs, Guidelines, manual etc.

AGENDA ITEM XVII:

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

Decision:

The CSC after detailed deliberation and discussion decided to delegate the following powers to Chairman CSC for smooth functioning of the Clinical Research under Rule 13(9) of The Bio-Study Rules, 2017:

Sr.	***Powers / Functions***	***Delegated powers***
i.	*Panel Constitution for inspection of CRO/BA&BE Center/Clinical Trial Site/Analytical Laboratory/Clinical Trial Study/BA&BE Study----prior to grant of license/approval and after approval for monitoring purpose.*	*Already delegated in 38th CSC meeting*
ii.	*Stoppage / Holding of Clinical Trial in case of emergency / untoward event of SAE.*	*Delegated powers and case will be placed before CSC in forthcoming meeting for deliberations (Resumption/suspension/cancellation).*
iii.	*Amendment in Protocol of Clinical Trial.*	** Delegated powers for minor amendments only.*
iv.	*Amendment in Investigator Brochure(IB).*	*Delegated.*
v.	*Amendment in Informed Consent Form (ICF).*	*** Delegated powers for minor amendments only.*
vi.	*Extension in Clinical Trial duration after approval from NBC.*	*Delegated.*
vii.	*Approval/Change of Technical Staff.*	*Delegated.*
viii.	*Approval to import of quantity of IMP as per approved protocol.*	*Delegated.*
ix.	*Destruction / re-export of unused / expired IMP after Clinical Trial.*	*Delegated.*

2. The applicant will submit the request in the Division of Pharmacy Services & same will be processed by the Secretariat (Pharmacy Services Division) and the Chairman will decide the matter as per powers delegated in above table.

***** Amendments which are unlikely to impact on participant safety like addition of laboratory test(s), statistical analysis, typographic corrections, updating contact point for trial participants, advertisement material / procedure, insurance detail / change of insurance provider.

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