# MINUTES OF THE 45TH CLINICAL STUDIES COMMITTEE MEETING (SUMMARY)

Pharmacy Services Division, Drug Regulatory Authority of Pakistan

File No: 16-45/2023-CSC (PS)

**OCTOBER 13, 2023**

**DRUG REGULATORY AUTHORITY OF PAKISTAN**

**Prime Minister's National Health Complex, Park Road, Chak Shahzad, Islamabad**

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45th meeting of the Clinical Studies Committee was held on 13th October, 2023 in the Committee room, Drug Regulatory Authority of Pakistan Head Quarter, 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 and Emerging Sciences, Peshawar, Khyber Pakhtunkhwa. | Member |
| iii. | **Dr. Mirza Tasawer Baig** | Associate Professor in the Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi and Clinical Pharmacist at Dr. Ziauddin Hospital, Karachi, Sindh. | Member |
| iv. | **Dr. Faiza Bashir** | Nominee of Chairman, Pakistan Health Research Council, Islamabad. | 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. Dr. Saeed Ahmad Khan** | Professor of Medicine Bolan Medical College Quetta presently serving as head of Medicine Department Jhalawan Medical College Khuzdar, Balochistan. | Member |
| ii. | **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 and Shafqat Hussain Danish assisted the Committee and Secretary in presentation of the agenda.

**AGENDA ITEM I:**

**CONFIRMATION OF THE MINUTES OF THE 44th CLINICAL STUDIES COMMITTEE MEETING.**

The minutes of the 44th CSC meeting held on 25th August, 2023. Minutes were shared with CSC members through email/ what's app. The CSC members submitted their consent and no comments/queries were received from the members. Accordingly, decisions of the meeting have been communicated and are placed for confirmation by members.

2. Submitted for confirmation of CSC Members.

**Decision:**

*All the Members of the CSC confirmed the Minutes of 44th CSC meetings.*

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**AGENDA ITEM II:**

**APPLICATION FOR LICENSE TO ACT AS CLINICAL TRIAL SITE FROM M/S PAK EMIRATES MILITARY HOSPITAL RAWALPINDI F. No.15-10/2022 DD (PS).**

The Case was presented before CSC. The Committee decided the case as follows:

*"The CSC after detailed discussion and deliberation and as per panel the recommendation decided to approve Clinical Trial Site (CTS) Situated at Pak. Emirates Military Hospital, Rawalpindi to act as CTS for phase III and IV clinical trials".*

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**AGENDA ITEM III:**

**APPLICATION FOR APPROVAL OF APPLICATION TO ACT AS CRO AT M/S KAMAL LABORATORIES, RAWALPINDI F. No.15-39/2023-CRO.**

The Case was presented before CSC. The Committee decided the case as follows:

*The CSC after detailed discussion and deliberation and as per panel report decided to defer the firm to act as CRO due to following reasons/shortcomings:*

i. *Establishment of Archiving room.*
ii. *Improvement of data security and Safety management cell.*
iii. *Hiring of Biostatistician.*
iv. *GCP and other trainings of the team.*

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**AGENDA ITEM IV:**

**APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "A MULTICENTER, RANDOMIZED, CONTROLLED, OPEN-LABEL PHASE IIB STUDY TO ASSESS EFFICACY AND SAFETY OF HH-003 INJECTION IN SUBJECTS WITH CHRONIC HEPATITIS DELTA VIRUS INFECTION (HH-003-204)", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-45/2023-CT (PS)**

The Case was presented before CSC. The Committee decided the case as follows:

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

i. *Approve the Phase-IIb Clinical Trial titled, "A Multicenter, Randomized, Controlled, Open-label Phase IIb Study to Assess Efficacy and Safety of HH-003 Injection in Subjects with Chronic Hepatitis Delta Virus Infection" under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site(s) and Trial Registration letter on Form-VI will be issued after provision of copy of signed MTA:*
    a. *Aga Khan University Hospital, Karachi (CTS-0003)*

ii. *Following site(s) will be included as additional sites after their approval from CSC for Phase-II Clinical Trial(s).*
    a. *The Central Park Teaching Hospital, Lahore.*
    b. *Ziauddin University Hospital, Karachi*

iii. *Approve the following quantities of IMPs, Lab Kits (for Sample Collection) and Ancillary items to be imported:*

***IMP Calculation:***

| ***Name of IMP*** | ***Quantity of IMP required for one (1) patient*** | ***Quantity of IMP required for 24 patients in treatment groups*** | ***Total Quantity of IMP required (including 25% overage)*** |
|---|---|---|---|
| *HH-003 300 mg/6rnl/vial* | *Treatment Group 1:<br>Assuming an avg patient wt is 100kg<br>20mg/kg X 100kg=2,000mg<br>300mg= 1 vial<br>2000mg=7 vials<br>7 vials/cycle/patient X 24 cycle<br>= 168 vials/patient* | *Treatment Group 1:<br>168 vials/patient x 12 Patients=2,016 vials* | *3,168 X l25%=3,960 vials* |
| | *Treatment Group 2:<br>Assuming an avg patient wt is 100kg<br>10mg/kg X 100kg=1,000mg<br>300mg= 1 vial<br>1000mg=4 vials<br>4 vials/cycle/patient X 24 cycle<br>= 96 vials/patient* | *Treatment Group 2:<br>96 vials/patient x 12 Patients=1,152 vials* | |
| | ***Total*** | ***3,168 Vials*** | ***3,960 Vials*** |

***Tenofovir alafenamide Details:***

| ***Name of IMP*** | ***Per patient dose*** | ***Frequency*** | ***Total*** |
|---|---|---|---|
| *TAF<br>Tenofovir alafenamide (Vemlidy®)<br>VEMLIDY tablets containing 25 mg of tenofovir alafenamide are yellow, round, film-coated, debossed with "GSI"' on one side and "25" on the other side.<br><br>Each bottle contains 30 tablets (NDC 61958-2301-l), a silica gel desiccant, polyester coil, and is closed with a child resistant closure.<br>Each bottle will be labeled as required per country requirement.* | *25 mg (1 Tablet)* | *Estimated screening of 50 subjects, 20% of whom will need to enter the NrtIs pre-treatment phase and undergo 12w TAF<br><br>Subjects will receive 25 mg (l tablet) orally once daily for 48 weeks during the treatment period and for 24 weeks during the follow up period total :72w).* | *50 x 20%:10 subjects NrtIs pre-treatment)<br><br>Assume dispensing 1 bottles per 4 weeks.<br><br>NrtIs pre-treatment:<br>3 bottles/subject x l0 subjects=30 bottles<br><br>**Treatment:**<br>12 bottles /subjects * 30 subjects=360 bottles<br>**Follow up:**<br>6 bottles/subject * 30 subjects: 180 bottles<br><br>**Total: 570 bottles*** |

***Wastage and Damage % will be 25%:***
*TAF: 570 x 25% = 143; Total Quantity: 570 + 143 = 713 Bottles*

*Manufacturer's name and address as per COA and GMP:*
*Manufacturer: Patheon Inc. 2100 Syntex Court, Mississauga, Ontario LsN 7K9 Canada*
*Batch and Expiry:*
*CNKCZ, 25-Oct-2026*

*CMYWY,22-Aug-2026*
*Packaging site and address:*
*Primary packing site: Patheon Inc. (Toronto, Canada)*

***Lab Kits and Ancillary Details:***

*a) Lab Kits:*

| ***Description*** | ***Qty*** | ***Description*** | ***Qty*** |
|---|---|---|---|
| *Kit A – Screening* | *117* | *Kit-M- Treatment Group Drug Resistance* | *16* |
| *Kit B - NrtIs Pre-Treatment* | *71* | *Kit-N - Treatment Group Early Term* | *16* |
| *Kit C - Treatment Group V1 W0* | *32* | *Kit-O-Treatment Group Unscheduled* | *16* |
| *Kit D - Treatment Group V3 W4* | *32* | *Kit-P - Control Group V1 W0* | *78* |
| *Kit E - Treatment Group V5 W8* | *32* | *Kit-Q-Control Group V 3N 4N 6N 7 EUZEU3* | *47* |
| *Kit F-Treatment Group Inten PK V7 W12* | *32* | *Kit-R - Control Group V8A/10 EOT/FU5* | *24* |
| *Kit G-Treatment Group PK V7 Wl224l48H* | *63* | *Kit-S - Control Group V5N9\|FU4* | *24* |
| *Kit H - Treatment Group Y9Nll/FU3* | *94* | *Kit-T - Control Group Drug Resistance* | *04* |
| *Kit I - Treatment Group Vl3 W24* | *32* | *Kit-U-Control Group Term* | *04* |
| *Kit J - Treatment Group V25 EOT/IU5* | *63* | *Kit-V - Control Group Unscheduled* | *04* |
| *Kit K - Treatment Group YI9EU4* | *63* | *Kit-W - Control Group Unscheduled* | *04* |
| *Kit L - Treatment Group FU2W52* | *32* | | |

*b) Ancillary items:*

| *S. No.* | *Description* | *Qty* | *S. No.* | *Description* | *Qty* |
|---|---|---|---|---|---|
| *i.* | *Absorbent Tube Holder, 6 Bay* | *4* | *viii.* | *Vacutainer, K2 EDTA, Plastic, 3mL* | *4* |
| *ii.* | *Bag, Specimen Shipping, 95kPa, (7x12in)* | *4* | *ix.* | *Vacutainer, K2 EDTA, Plastic,4mL* | *4* |
| *iii.* | *Cryovial, NUNC, Round Bottom, Internal Thread, 4.5mL* | *4* | *x.* | *Vacutainer, K2 EDTA, Plastic 6mL* | *4* |
| *iv.* | *Investigator Manual (Color)* | *4* | *xi.* | *Vacutainer, SST II, Plastic, 6mL* | *4* |
| *v.* | *Micro Tube, Sarstedt, Graduated, Sterile,2mL* | *4* | *xii.* | *Vacutainer, SST, Plastic ,2.5mL* | *4* |
| *vi.* | *Standard Pipette, Transfer* | *4* | *xiii.* | *Vacutainer, SST, Plastic, 3.5mL* | *4* |
| *vii.* | *Tube, Sarstedt, Transfer, False Bottom, Graduated 2.5nn-* | *4* | *xiv.* | *Vacutainer, SST, Plastic, 5mL* | *4* |

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**AGENDA ITEM V:**

**APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "A PHASE 3, RANDOMIZED, OBSERVER-BLIND, CONTROLLED, MULTICENTER, CLINICAL STUDY TO EVALUATE IMMUNOGENICITY AND SAFETY OF A HIGH-DOSE MF59 ADJUVANTED QUADRIVALENT SUBUNIT CELL-DERIVED INFLUENZA VACCINE (aQIVc HD) IN COMPARISON WITH A NON-ADJUVANTED QUADRIVALENT RECOMBINANT INFLUENZA VACCINE (QIVr) AND AN MF59-ADJUVANTED QUADRIVALENT SUBUNIT EGG-DERIVED INFLUENZA VACCINE (aQIV), IN ADULTS AGED 50 YEARS AND OLDER", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-46/2023-CT (PS)**

The Case was presented before CSC. The Committee decided the case as follows:

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

*i. Approve the Phase-III Clinical Trial titled, "A Phase 3, Randomized, Observer-Blind, Controlled, Multicenter, Clinical Study to Evaluate Immunogenicity and Safety of a MF59-Adjuvanted Quadrivalent Subunit Cell-derived Influenza Vaccine (aQIVc) in Comparison with Quadrivalent Influenza Vaccines, in Adults Aged 50 Years and Older." under the Bio-Study Rules, 2017, to be conducted at following Clinical Trial Site(s) and Trial Registration letter on Form-VI will be issued after provision of copy of signed MTA:*

   *a. Aga Khan University, Karachi*
   *b. The Central Park Teaching Hospital, Lahore.*

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

| ***IMPs*** | ***Molecule*** | ***Strength*** | ***Pack Size*** | ***Manufacturer*** | ***TOTAL*** |
|---|---|---|---|---|---|
| *aQIVc HD* | *Adjuvanted Quadrivalent Influenza Vaccine (aQIV)* | *Containing 45µg HA/strain and 19.5 mg squalene (MF59* | *1 Syringe – 1.0 ml, formulated in* | *Seqirus Inc., 475 Green* | *214* |

| | | | | | |
|---|---|---|---|---|---|
| | *influenza vaccine is a sterile preparation of four purified influenza virus antigens in an isotonic buffer solution, combined with the MF59 adjuvant, for Intramuscular administration. aQIV is provided in a pre-mixed format in syringes and contains the antigens of two type A strains and two type B strains* | *adjuvant), in a total volume of 1.0 ml, formulated in a prefilled syringe (PFS)* | *a prefilled syringe / per kit.* | *Oaks Parkway Holly Springs, NC 27540, USA* | |
| *QIVr* | *Supemtek Quadrivalent is a vaccine indicated for active immunization against disease* | *Containing 45µg HA/strain (non-adjuvant), in a total volume of 5.0 ml, formulated in a prefilled syringe (PFS)* | *1 Syringe – 0.5 ml, formulated in a prefilled syringe / per kit.* | *Sanofi Pasture, Lyon France.* | *143* |
| *aQIV* | *FLUAD QUADRIVALENT is an inactivated influenza vaccine indicated for active immunization against influenza disease caused by influenza virus subtypes A and types B contained in the vaccine.* | *Containing 15µg HA/strain and 9.75 mg (non-adjuvant), in a total volume of 5.0 ml, formulated in a prefilled syringe (PFS)* | *1 Syringe – 1.0 ml, formulated in a prefilled syringe / per kit.* | *Seqirus Netherlands B.V.* | *143* |
| *Repackaged and relabeled by M/s Catalent Pharma Solutions, LLC, Philadelphia, PA19154, USA.* | | | | | |

### *IMP Calculation: Treatment Plan:*

| ***IMP*** | ***No. of Patients*** | ***Per Patient Dose*** | ***Frequency*** | ***Total*** |
|---|---|---|---|---|
| *aQIVc HD* | *214* | *1* | *1* | *214* |
| *QIVr* | *143* | *1* | *1* | *143* |
| *aQIV* | *143* | *1* | *1* | *143* |

***Wastage and Damage % will be 100%*** *(justification is part of this document why 100% is required):*

*Active aQIVc HD: 214 * 100% = 214; Total Import Quantity: 214+ 214 = 428*
*Comparator QIVr: 143 *100% = 143; Total Import Quantity: 143+ 143 = 286*
*Comparator aQIV: 143 *100% = 143; Total Import Quantity: 143+ 143 = 286*

### *Source of IMPs:*

| ***IMPs*** | ***Site*** | ***Role*** | ***Address*** |
|---|---|---|---|
| *aQIVc HD* | *Seqirus Inc US* | *Manufacturer and MAH* | *Seqirus Inc., 475 Green Oaks Parkway Holly Springs, NC 27540, USA* |
| | *Catalent Pharma US* | *Repacker* | *Catalent Pharma Solutions, LLC, 10381 Decatur Road, Philadelphia, PA 19154, USA* |
| | *Seqirus Inc US* | *Release* | *Seqirus Inc., USA* |
| *aQIV* | *Seqirus Inc US* | *Manufacturer and MAH* | • *Seqirus Inc., 475 Green Oaks Parkway Holly Springs, NC 27540 USA.*<br>• *Seqirus Netherlands B.V., Paasheuvelweg 28. 1105 BJ Amsterdam. The Netherlands* |
| | *Catalent Pharma US* | *Repacker* | • *Catalent Pharma Solutions, LLC, 10381 Decatur Road Philadelphia, PA 19154 USA.*<br>• *Catalent Pharma Solutions-SNG Pte. Ltd., No. 1 Jalan Kilang #02-01 Singapore, 159402* |
| | *Seqirus Inc US* | *Release* | *Seqirus Inc.,475 Green Oaks Parkway Holly Springs, NC 27540 USA* |
| *QIVr FLUBLOK* | *Protein Sciences US* | *Manufacturer* | *Protein Sciences US, 1000 Research Parkway, Meriden, Connecticut 06450, United States* |
| | *Sanofi Pasteur US* | *MAH* | *Sanofi Pasteur US, 1 Discovery Drive, Swift water Pennsylvania 18370, USA* |
| | *Catalent Pharma US* | *Repacker* | *Catalent Pharma Solutions, LLC, 10381 Decatur Road Philadelphia, PA 19154, USA* |
| | *Seqirus Inc US* | *Release* | *Seqirus Inc., 475 Green Oaks Parkway Holly Springs, NC 27540, USA.* |
| ***QIVr (Supemtek)*** | *Sanofi Pasteur Aventis Pharma Limited trading as Sanofi Pasteur* | *Manufacturer and MAH* | *Sanofi Pasteur, Parc Industriel d'Incarville, 27100 Val de Reuil, France*<br>*Aventis Pharma Limited trading as Sanofi Pasteur (License Numbers: PLGB 04425/0879)*<br>*410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK.* |

| | | | |
|---|---|---|---|
| | *Catalent Pharma Solutions-SNG* | *Repacker* | *Catalent Pharma Solutions-SNG*<br>*Pte. Ltd. No. 1 Jalan Kilang #02-01, Singapore, 159402* |
| | *Seqirus Inc US* | *Release* | *Seqirus Inc.*<br>*475 Green Oaks Parkway Holly Springs, NC 27540*<br>*USA* |

***Batch and Expiry:***
*Blinded Batch Number on kits: 20103039 / Blinded Expiry on kits: 02/2024*
*Active: Batch aQIVc HD # 20103039; 02/2024*
*Comparator QIVr (Flublok®): Batch# 20103039; 02/2024*
*Comparator QIVr (Supemtek UK): Batch# QFAA2303; 05/2024*
*Comparator aQIV (Fluad Tetra US): Batch# 20103039; 02/2024*
*Comparator aQIV (Fluad Tetra EU): Batch# 3029515; 04/2024*

***Packaging site and address:***
*Catalent Pharma solutions*
*3031 Red Lion Road*
*Philadelphia PA 19114, USA*
*Catalent Pharma Solutions-SNG*
*Pte. Ltd., No. 1 Jalan Kilang #02-01*
*Singapore, 159402*
*Singapore.*

***Ancillary Supplies:***

| ***Item Description*** | ***Quantities*** | ***Justification*** |
|---|---|---|
| *25G x 1" needle 100x box* | *8 boxes* | *2 sites x 2 =4 + 100% buffer = 8* |
| *25G x 1 1/2" needle 100x box* | *8 boxes* | *2 sites x 2 =4 + 100% buffer = 8* |

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**AGENDA ITEM VI:**

**APPLICATION FOR AMENDMENT IN ALREADY APPROVED 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).**

The Case was presented before CSC. The Committee decided the case as follows:

*The CSC after deliberation and discussion decided to approve the amendments in following documents of already approved 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".*

i. *Details of amended documents is as follows:*

| *S.No.* | *Documents* | *Current/Amended Version* | *Dated* |
|---|---|---|---|
| *1* | *Trial Protocol PRO-sIPV-4001* | *3.3* | *28th July,2023* |
| *2* | *Master Information Sheet and ICF for Adult (English/Urdu)* | *3.3* | *28th July,2023* |
| *3* | *Master Information Sheet and ICF for Parent/LAR (English/Urdu)* | *3.3* | *28th July,2023* |
| *4* | *Diary Card (English/Urdu)* | *1.2* | *28th July,2023* |
| *5* | *Site Worksheet/CRF* | *2.0* | *28th July,2023* |

**AGENDA ITEM VII:**

**APPLICATION FOR AMENDMENT IN ALREADY APPROVED CLINICAL TRIAL TITLED "RANDOMIZED CONTROLLED TRIAL TO ASSESS THE IMMUNOGENICITY AND SAFETY OF FULL VERSUS FRACTIONAL DOSE OF PFIZER/BIONTECH, ASTRAZENECA, AND SINOVAC COVID-19 VACCINES GIVEN AS A BOOSTER DOSE AT LEAST 6 MONTHS AFTER PRIMARY VACCINATION SERIES OR PCR-CONFIRMED INFECTION WITH SARS-COY-2 IN HEALTHY ADULTS", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-08/2022-DD (PS)**

The Committee after discussion decided the case as follows:

a. *Acknowledged the progress report.*
b. *Approved the amendments in following documents of already approved Clinical Trial titled, "Randomized Controlled Trial to Assess the Immunogenicity and Safety of Full Versus Fractional Dose of Pfizer/BioNTech, AstraZeneca, And Sinovac Covid-19 Vaccines Given as A Booster Dose at Least 6 Months After Primary Vaccination Series or PCR-Confirmed Infection with Sars-Coy-2 In Healthy Adults":*

i. *Study Protocol (Version-5)*
ii. *ICF_NI_arm English (Version-1)*
iii. *ICF_NI_arm Urdu 13-05-2023 (Version-1)*
iv. *ICF Urdu, dated 13-05-2023 (Version-6)*
v. *ICF Urdu, dated 13-05-2023 (Version-6)*
vi. *Eligibility Screening CRF (One Amendment) (Version-2)*

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**AGENDA ITEM VIII:**

**APPLICATION FOR AMENDMENT APPROVAL OF CLINICAL TRIAL TITLED "A PHASE-III, MULTICENTRE. RANDOMIZED, DOUBLE-BLIND, 24-WEEK STUDY OF THE CLINICAL AND ANTIVIRAL EFFECT OF S-217622 COMPARED WITH PLACEBO IN NON-HOSPITALIZED PARTICIPANTS WITH COVID-19", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-25/2023-CT (PS)**

The Case was presented before CSC. The Committee decided the case as follows:

*The CSC after detailed deliberation and discussion decided to approve following points:*

a. *the protocol amendments (Version 5, dated 24 February 2023), as well as study Informed Consent Forms and Patient Documents and increase in enrollments (from 84 to 500) of already approved Clinical Trial titled, "A Phase-III, Multi-Centre. Randomized, Double-Blind, 24-week Study of the Clinical and Antiviral Effect of S-217622 Compared with Placebo in Non-Hospitalized Participants with COVID-19" as per following details:*

I. *Substantial Amendment: Protocol Amendment Version 5, dated 24 February 2023 and Informed Consent Forms/Patient Documents - submitted to DRAP on 27-Jun-2023.*

***Protocol Related***

i. *Protocol Version 5, dated 24February 2023*
ii. *Protocol Version 5, track changes V3 v V5, dated 24 February 2023*
iii. *Protocol Version 5 track changes V4 v V5, dated 24 February 2023*
iv. *Summary of Changes, Version 5 dated 24 February 2023*
v. *Protocol Version 4, dated 17 February 2023*
vi. *Protocol Version 4, track changes V3 v V4, dated, 17 February 2023*
vii. *Summary of Changes, Version 4 dated 17 February 2023*
viii. *ACTIV-2d_A5407- Protocol Admin Letter PK sampling V1 26 April 2023*
ix. *ACTTV-20_A5407_Main ICF V 6.0 dated 10 March 2023_Pak V3.0 dated 30 May 2023-clean (Eng, Urdu and Tcert)*

x. *ACTTV-2D_A5407_Main ICF V 6.0 dated 10 March 2023-Pak V3.0 dated 30 May 2023-track changes*

***Investigator Documents***

i. *Investigator Letter, Version 01, dated 29 July 2022*
ii. *Key Eligibility criteria checklist, Version 01., dated 29 August 2022*

***Patient Documents***

i. *Participant Flyer, Version 02, dated 27 April2023 (Eng, Urdu and Tcert)*
ii. *Background to Treatment Flyer, dated 10 March 2023*
iii. *Medication log V3.0 dated 27 March 2023 (Eng, Urdu and Tcert)*
iv. *Participant Brochure V02, dated 27 April 2023 (Eng, Urdu and Tcert)*
v. *Participant Poster V02, dated 27 April 2023 (Eng, Urdu and Tcert)*
vi. *Participant Study Drug Instruction Card V02, dated 14 April 2023 (Eng, Urdu and Tcert)*
vii. *Physician Referral Letter V02, dated 25 May 2023 (Eng, Urdu and Tcert)*
viii. *IQVIA eCOA patient Manual Shionogi ACTIV 2d A5407-V2.0 dated 19 September 2022*
ix. *(English)*
x. *eCRF Version 6.0 dated 06 June 2023*
xi. *eCRF Version 7.0 dated 19 June 2023*
xii. *ACTIV-2D SCORPIO-H R Toolkit*

II. *Submission of FINN patient-facing materials to raise awareness of SCORPIO-HR in Pakistan and Notification of latest eCRF V7.0 dated 19June2023 - Submitted on 18-Aug-2023*

***Purpose / description of patient-facing materials to raise awareness of SCORPIO-HR in Pakistan:***

i. ***English poster, ON SITE:*** *Digital and printed material in English to be used to produce posters and standees for individual research sites / to be used on the hospital premises.*
ii. ***English Poster, OFF SITE:*** *Digital and printed material in English to be used to produce posters and standees to be displayed in laboratories, pharmacies, and other locations near research sites as well as to produce a flyer and a cable advertisement.*

***Urdu Translations:***

i. *ON SITE POSTER - 18 by 24_UR-PK: Digital and printed material in Urdu to be used to produce posters and standees for individual research sites /to be used on the hospital premises.*
ii. *OFF S\|TE POSTER - 18 by 24_UR-PK: Digital and printed material in Urdu to be used to produce posters and standees to be displayed in laboratories, pharmacies, and other locations near research sites as well as to produce a flyer and a cable advertisement.*

***Social Media Content:***

i. *Facebook Post: Social content to be posted on Facebook pages of individual research sites / hospitals with their contact information. Social content can be reposted by individual Facebook users.*
ii. *Twitter Post: Social content to be posted on Twitter profile of individual research sites / hospitals with their contact information. Social content can be reposted by individual Twitter users.*
iii. *Instagram Story: Social content to be posted on Instagram profile of individual research sites / hospitals with their contact information. Social content can be reposted by individual Instagram users.*
iv. *Instagram Feed: Social content to be posted on Instagram profiles of individual research sites / hospitals with their contact information. Social content can be reposted by individual Instagram users.*

b. *Application for Amendment/Increase in Subjects Enrollment and Increase in IMP Import -Submitted on 04-Aug-2023 Global enrolment 1490 to 2000 subjects (For Pakistan from 84 to 500)*

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**AGENDA ITEM IX:**

**Case-I**

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

The Case was presented before CSC. The Committee decided the case as follows:

*The CSC after deliberation and discussion decided to approve **Aga Khan Hospital for Women, Karim Abad Karachi (CTS-0061)** as an additional Clinical Trial Site for already approved Clinical Trial titled, "A Multi-Country, Multi-Center, Three-Arm, Parallel Group, Double-Blind, Placebo-Controlled, Randomized Trial of Two Doses of Antenatal Corticosteroids for Women with a High Probability of Birth in the Late Preterm Period in Hospital in Low-Resource Countries to Improve New-Born Outcomes".*

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**AGENDA ITEM X:**

**APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED, "A PHASE 2, OPEN-LABEL STUDY TO ASSESS THE SAFETY AND EFFICACY OF BEMNIFOSBUVIR (BEM) AND RUZASVIR (RZR) IN SUBJECTS WITH CHRONIC HEPATITIS C VIRUS (HCV) INFECTION" FROM THE AGA KHAN UNIVERSITY (AKUH), STADIUM ROAD, KARACHI. F.NO.03-47/2023-DD-CT-II(PS)**

*The CSC after detailed deliberation decided to defer the case for following reasons: -*

i. *Provide the complete data of Phase-I of the subject study;*
ii. *Provide the clarification about the actual manufacturer of the IMP and who will provide the IMPs. (Atea Pharmaceuticals Inc. and/or Patheon Pharmaceutical);*
iii. *Provide the name of Monitors and Clinical Research Associate;*
iv. *The following two sites, i.e., intended for clinical trial of the subject study does not contain the approval to conduct the phase-II studies;*
    a. *Ziauddin University Hospital 4/B, Shahrah-e-Ghalib Rd. Block 6 Clifton, Karachi.*
    b. *Central Park Teaching Hospital, 31-km. Ferozpur Road, Kaha Nau, Lahore.*

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**AGENDA ITEM-XI:**

**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.03-38/2023-CT (PS)**
**Decision in 45th CSC Meeting:**

*The CSC after deliberations on the response submitted by the CRO decided to:*

i. *Revoke the suspension of 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", to continue and conclude study for the purpose of monitoring and follow-up activities as per approved protocol.*

ii. *Forward response of the law firm M/s Aspire Law, Karachi (Advocates & Corporate Counsel) regarding compensation to fatal cases to Legal Affairs Division of DRAP for their perusal and recommendations.*

iii. *Defer the amendment in protocol of the clinical trial till submission of approval from NBC and approval from IRB for two sites of SIDH and Dow University.*

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**AGENDA ITEM-XII**

**A MULTICENTER, OPEN LABEL, RANDOMIZED, PHASE-III, CLINICAL TRIAL TO EVALUATE EFFICACY AND SAFETY OF PF-114 VERSUS IMATINIB AT 600 mg OR 800 MG DAILY IN ADULT PATIENTS WITH PHILADELPHIA CHROMOSOME POSITIVE (PH+) CHRONIC MYELOID LEUKEMIA (CML) IN THE CHRNIC PHASE (CP) RESISTANT TO IMATINIB AT DAILY DOSES OF 400 mg OR 600 mg.**

The Case was presented before CSC. The Committee decided the case as follows:

**Decision in 45th CSC Meeting:**

The CSC after deliberation decided to*:*

***i.*** *Approve the Clinical Trial under the Bio-Study Rules 2017 to be conducted at following Clinical Trial Sites:*

| ***Site(s)*** | ***PI*** |
|---|---|
| *Ziauddin University Hospital, Karachi* | *Dr. Amna Qamar uz Zaman* |
| *Shifa International Hospital, Islamabad* | *Dr. M Ayaz Mir* |
| *Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad (SZABMU-PIMS)* | *Dr. Qasim Mahmood* |
| *Rehman Medical Institute, Peshawar* | *Dr. Humaira Taj* |
| *Indus Hospital & Health Network, Karachi* | *Dr. Zunaira Aamir* |

***ii.*** *Approve the following Investigational Medicinal Product (IMPs) with the direction to get Clearance Certificate from Import & Export department of DRAP.*

| ***Title*** | ***PF-114*** | ***Reference Drug*** |
|---|---|---|
| *Name* | *INN: Vamotinib* | *INN: Imatinib* |
| *Manufacturer* | *M/s JSC Pharmasyntez-Nord JSC Russia, Lit.A, 74, Doroga v Kamenku St., St. Petersburg, Russia.* | *M/s JSC Pharmasyntez-Nord JSC Russia, Lit.A, 74, Doroga v Kamenku St., St. Petersburg, Russia.* |
| *Dosage Form* | *Capsule* | *Film Coated Tablet* |
| *Strength* | *100 mg* | *100 mg* |
| *Quantity* | *1419 packs (30 capsules pack)* | *2351 packs (30 tablets pack)* |

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**AGENDA ITEM-XIII**

**INCLUSION OF ADDITIONAL SITE FOR ALREADY APPROVED CLINICAL TRIAL "A DOUBLE-BLIND, RANDOMIZED CLINICAL STUDY OF THE EFFICACY AND SAFETY OF BCD-178 AND PERJETA® AS NEOADJUVANT THERAPY OF HER2-POSITIVE BREAST CANCER (PREFER)" F.No.03-44/2023-CT (PS)**

**Decision in 45th CSC Meeting:**

The Case was presented before CSC. The Committee decided the case as follows:

*The CSC after deliberation decided to approve the following additional clinical trial Site for already approved clinical trial "A Double-Blind, Randomized Clinical Study of the Efficacy and Safety of BCD-178 and PERJETA® as Neoadjuvant Therapy of HER2-Positive Breast Cancer (PREFER)" under the Bio-Study Rules, 2017.*

| ***Site*** | ***PI*** |
|---|---|
| *Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad* | *Dr. Qasir Buttar* |

**AGENDA ITEM-XIV**

**APPLICATION FOR EXPORT OF UNUSED INVESTIGATIONAL PRODUCT (80 VIALS) TO SPONSOR IN RUSSIA FOR ALREADY APPROVED CLINICAL TRIAL "A RANDOMIZED, DOUBLE-BLIND CLINICAL STUDY OF THE EFFICAY AND SAFETY OF BCD-201 (JS BIOCAD) AND KEYTRUDA IN PATIENTS WITH UNRESECTABLE OR METASTATIC MELANOMA.**

The Case was presented before CSC. The Committee decided the case as follows:

**Decision in 45th CSC Meeting:**

***i.*** *The CSC acceded to the request to export unused investigational product (80 vials) to sponsor in Russia for already approved clinical trial "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." as per following details with the direction to get Clearance Certificate/NOC from Import & Export department of DRAP.*

| ***Name of Drug*** | ***Generic*** | ***Quantity to export*** | ***Company*** |
|---|---|---|---|
| *BCD-201/Keytruda* | *Pembrolizumab* | *80 Vials* | *JSC Biocad Russia* |

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**AGENDA ITEM-XV**

**REQUEST FOR APPROVAL OF AMENDMENT OF INVESTIGATOR BROCHURE VERSION 3.0 DATED MARCH 13, 2023, PROTOCOL AMENDMENT VERSION 4.0 OF JUNE 6, 2023 AND ICF AMENDMENT V3.0 PAK DATED AUGUST 08,2023 FOR ALREADY APPROVED CLINICAL TRIAL "A RANDOMIZED, DOUBLE-BLIND CLINICAL STUDY OF THE EFFICAY AND SAFETY OF BCD-201 (JS BIOCAD) AND KEYTRUDA IN PATIENTS WITH UNRESECTABLE OR METASTATIC MELANOMA.**

The Case was presented before CSC. The Committee decided the case as follows:

**Decision in 45th CSC Meeting:**

*The CSC after deliberation decided as follows;*

a. *to approve following amendments for sites except Jiannah and Mayo Hospital, Lahore due to non-submission of IRB approvals.*

i. *Clinical Study Protocol Version 4.0 June 06, 2023.*
ii. *Investigator's Brochure Version 3.0 of March 15, 2023.*
iii. *Informed Consent Form (English & Urdu) Version ICF V3.0 PAK dated 08 August 2023.*

b. Authorized Chairman, CSC to issue approval for conduction of clinical trial as per amended protocol at *Jiannah and Mayo Hospital, Lahore after their IRB approvals.*

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**AGENDA ITEM XVI:**

**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)**

The case was presented before CSC. The Committee decided the case as follows:

*The CSC after 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 15 days, after which the application will be placed before CSC for final decision.*

**AGENDA ITEM XVII:**

**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)**

The Case was presented before CSC. The Committee decided the case as follows:

*The CSC after deliberation and 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 and 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 and 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.*
iv. *It is mentioned that, USA, Vietnam and 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)*
v. *In reply of IMPs justification, it is claimed that, locally registered product Filgen will be utilized in Pakistan. Whereas, as per IND approval and US Trial Registry Nupogen have IND approval for the trial.*
vi. ***Anticipated cost of the project is n**ot provided.*
vii. *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.*
viii. *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.*
ix. *Pre-Clinical and Clinical studies are not provided and 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.*
x. *Sponsor status is not clear, [Holterman, Ai-Xuan, M.D. (Sponsor is a person instead of firm or manufacturer)]*
xi. *Summary of IB and Protocol are not provided.*
xii. *Evidence of registration in country of origin for Nupogen, is not provided and claimed that locally produced drug will be utilized.*
xiii. *Sample label also shows that the PI conducted the trial without approval as Manufacturing and Expiry dates are printed on the label.*
xiv. *Undertaking on Stamp paper is not provided.*

*2. Further, it is decided to grant a last opportunity to the applicant/PI to submit point-wise reply with all pre-requisites and prescribed fee, within 15 days, after which application will be placed before CSC for final decision.*

**AGENDA ITEM XVIII:**

**APPLICATION FOR AMENDMENT 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).**

The case was presented before CSC. The Committee decided the case as follows:

*The Committee after deliberations decided to defer the case for clarification as IMP (device) has been developed and assembled in a not for profit, academic research lab at the Massachusetts General Hospital in Boston, MA, USA and don't have any GMP certification.*

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