DRUG REGULATORY AUTHORITY OF PAKISTAN

مانیٹرل امراض کا یاد ون دوا

محفوظ مونثر معیاری

MINUTES OF 57TH MEETING OF CLINICAL STUDIES COMMITTEE HELD ON 20th MAY, 2025.

Division of Pharmacy Services
Drug Regulatory Authority of Pakistan
Islamabad.

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4.	**Amendments/Miscellaneous applications**	**---**	**---**
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4.2	APLICATION FOR APPROVAL OF PROTOCOL AMMEMDMENT VERSION 5.0 AND ASSOCIATED DOCUMENTS FOR ALREADY APPROVED CLINICAL TITLE "A PHASE II, RANDOMIZED, OBSERVER-BLINDED, PLACEBO CONTROLLED TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF HECOLIN ® IN HEALTHY PREGNANT WOMEN BETWEEN GESTATIONAL AGE 14-34 WEEKS AND NON-PREGNANT WOMEN OF 16-45 YEARS OLD". **F.NO.03-35/2023-DD(PS)**	**DD-CR-II**	**127-140**
5.	**Miscellaneous Agenda Item**	**---**	**---**
5.1	REVISION OF FOLLOWING GUIDELINES DEVELOPED UNDER THE BIO-STUDY RULES, 2017 (**F.NO.03-35/2023-DD(PS)**): i. Guidelines for Conduct of Clinical Research in Pakistan. (3rd Revision) ii. Guidelines for Conduct & Reporting of GCP Inspections (3rd Revision)		
5.2	APLICATION FOR RENEWAL/ EXTENSION OF DRAP APPROVAL FOR ALREADY APPROVED CLINICAL TITLE "A PHASE II, RANDOMIZED, OBSERVER-BLINDED, PLACEBO CONTROLLED TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF HECOLIN ® IN HEALTHY PREGNANT WOMEN BETWEEN GESTATIONAL AGE 14-34 WEEKS AND NON-PREGNANT WOMEN OF 16-45 YEARS OLD". **F.NO.03-35/2023-CT (PS)**		
5.3	REQUEST FOR CONSIDERATION REGARDING CRO - DRK PHARMA: SITE FEE CLEARANCE ISSUE IMPACTING OPERATIONAL AND PATIENT SAFETY STANDARDS. **F.NO.08-07/2025-MISC (PS))**		

57th meeting of the Clinical Studies Committee was held on 20th May, 2025 in the Committee Room of Drug Regulatory Authority of Pakistan, NCLB Building, Prime Minister's National Health Complex, Park Road, Chak Shahzad, Islamabad. The meeting was chaired by Mr. Abdullah, Director, Division of Pharmacy Services, DRAP. The meeting started with the recitation of the verses from the Holy Quran.

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

S. No.	Name	Designation
1.	Abdullah, Director Pharmacy Services Division-DRAP.	Ex-Officio Chairman
2.	Dr. Faiza Bashir, Chairman, Pakistan Health Research Council, Islamabad.	Member
3.	Prof. Dr. Mirza Tasawer Baig, Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi and Clinical Pharmacist at Dr. Ziauddin Hospital, Karachi, Sindh.	Member
4.	Mr. Malik Muhammad Asad, Deputy Director, Pharmacy Services Division-DRAP.	Ex-officio Secretary

3. The following members attended the meeting online via Zoom.

1.	Prof. Dr. Fazal Subhan, Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar, (Khyber Pakhtunkhwa).	Member
2.	Prof. Dr. Saeed Ahmad Khan, Professor of Medicine Bolan Medical College Quetta presently serving as head of Medicine Department Jhalawan Medical College Khuzdar, Baluchistan.	Member
3.	Mr. Waqas Latif, Data Analyst/Biostatistician in Quality Enhancement Cell (QEC) at the University of Health Sciences, Lahore, Punjab.	Member

Dr. Mahvash Ansari, Deputy Director, Mr. Hafiz Muhammad Umair Deputy Director and Mr. Shafqat Hussain Danish Deputy Director assisted the Committee and the Secretary in presentation of the agenda and recording of minutes of the meeting.

AGENDA ITEM-1: CONFIRMATION OF MINUTES

CONFIRMATION OF THE MINUTES OF THE 56TH MEETING OF CLINICAL STUDIES COMMITTEE.

The 56th meeting of the Clinical Studies Committee was held on 29th April 2025. The draft minutes of the meeting were shared with CSC members through email. The CSC members submitted their consent and no comments/queries were received from the members.

2. Accordingly, fair minutes of the meeting were submitted to the Chairman CSC for approval and signatures. After approval of the minutes, decisions taken in the meeting were communicated to the applicants.

3. Minutes of the 56th CSC meeting were placed before the Committee for confirmation.

Decision: The CSC confirmed the minutes of the 56th meeting.

AGENDA ITEM-2: GRANT/RENEWAL OF LICENSE TO ACT AS BA/BE CENTER, CLINICAL TRIAL SITE, CRO OR LABORATORY

CASE No. 2.1:

APPLICATION FOR LICENSE TO ACT AS CLINICAL TRIAL SITE FOR PHASE III & IV FROM PREMIUM MEDICAL COMPLEX (PVT.) LTD., RAWALPINDI F. No. 15-71/2024-CTS.

Application is received from Dr. Brig (R) Ishaq Ahmad Qureshi, Medical Director, of M/s Premium Diagnostic Rawalpindi, 02 The Mall, Saddar Rawalpindi Cantt., 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/- submitted vide slip number 79986585 dated 15th May 2024.

2. The application has been 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 of Rs.100,000/- submitted vide slip number 79986585 dated 15th May 2024.
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).	Following documents are enclosed; SECP certificate of Incorporation, PHC Registration Certificate, BS EN ISO 9001:2015 attached. Also Excise and Taxation Department Certificate of Registration, IHRA Registration Certificate, RICI ISO 9001:2015, Taxpayer Certificate issued to Premium Diagnostic Center Islamabad attached. **Name of the Firm is Premium Diagnostic Center as per SECP Certificate of Incorporation and Excise and Taxation Department Certificate of Registration and Name on Form-I is Premium Diagnostic. Clarification**

		required.
4	Details of premises including layout plan of the site.	The 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.	CVs attached
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	SOP for Medical & Fire Emergency and Natural Calamities attached.
8	Undertaking on stamp paper	Attached.

3. The applicant vide letter No. nil dated 6th August, 2024, in response to this Division's letter No. 15-17/2024-CTS dated 1st July, 2024 responded to the shortcomings in the application. The clarifications sought along with applicant's response is summarized as under: -

SHORTCOMINGS COMMUNICATED	REPLY BY THE APPLICANT
Name of the firm is Premium Diagnostic Center as per SECP Certificate of Incorporation and Exercise and Taxation Department Certificate of Registration, whereas name mentioned on Form-I is Premium Diagnostic clarification is required.	Title of the proposed site is changed to "PREMIUM MEDDICAL COMPLEX (PVT.) LTD" which is relocated to Javed Lane, Main Peshawar Road Saddar Rawalpindi. Certificate of Incorporation by SECP (ID No. 0222981) has been provided.
Role of a Al Ihsan Hospital and Mariam Hospital in this CTS need to be explained.	The hospital is equipped with an emergency setup for ambulatory care and as affiliated with an Al- Ihsan Hospital and Mariam Hospital to manage additional emergency patients a necessary. Additionally the stakeholders of Premium Diagnostic Hospital have established a diagnostic laboratory in Islamabad under the same name Premier Diagnostic Laboratory therefore they provide these about your services to both a Al -Ihsan and Marine Hospital.

4. The chairman CSC constituted the following panel of experts for inspection of Trial Site:

i. Dr. Faiza Bashir Member CSC.
ii. Malik Muhammad Asad Deputy Director Pharmacy Services Division DRAP Islamabad
iii. Shafqat Hussain Danish Deputy Director Pharmacy Services Division DRAP Islamabad

5. The nominated panel inspected the premises on 27-03-2025. The inspection report is as reproduced as under: -

✓ **Panel report**

CLINICAL TRIAL SITE (CTS) INSPECTION CHECKLIST

Name of facility: ***Premium Medical Complex***
Address: ***Main Peshawar Road Rawalpindi***
Organization Type: ☐ *Public* ☐ *Not for Profit* ■ *Private* ☐ *Other-* _____
Name of Owner / Proprietor: ***Dr. Ishaq Ahmed Qureshi***
Date of inspection: ***27.03.2025*** *(dd/mm/yyyy)*

i. General Information	*Yes*	*No*	*NA*	*Observations / Recommendations*
Is this CTS a primary care, secondary care or tertiary care facility? (Record one in observations section)	✓			*Tertiary Care*
Is this the Composite CTS (Where Principal			✓	*New license, no trial conducted*

investigator is located)?				
Is the facility registered with the Healthcare Commission?	✓			
If yes, is the certificate, available for review and is valid?				
Is there enough space available for proper functioning for clinical trials?				
Is there an outpatient facility?	✓			
If yes, On an average how many patients visit per day?				
Is there an inpatient facility?	✓			
If yes, how many beds?				
Have any clinical trials been conducted at this CTS in the past?			✓	*New facility*
If yes, how many clinical trials were conducted? Give details of the PI as well as nature and duration of the clinical trials.			✓	
How many other studies currently ongoing at the site? If yes, how many clinical trials were conducted? Give details of the PI as well as nature and duration of the clinical trials.	✓			
Is there a pharmacy / dedicated investigational Medicine dispensing area?	✓			*Panel suggested improvements regarding entry/exit (access) control and environmental controls.*
If yes, does the CTS have required storage facility for routine operations?	✓			
If yes, does the CTS have required trial related Investigational Product storing facility? (Investigational Product Provided by the sponsor as per requirements of the protocol).	✓			
Does the CTS have Laboratory services?	✓			
If yes, is in-house or central?	✓			
Is there an X-Ray facility?	✓			
If yes, is it on-house or central?	✓			
Does the facility have an incinerator? If yes, document the average weight of Hospital waste disposed of per month.		✓		
If No, does the facility, have a contract with a Hospital waste management Company?	✓			*Contract with waste management company*
ii. Study Related Staff	***Yes***	***No***	***NA***	***Observations / Recommendations***
Does the CTS have, any of the study related personnel on staff? *-Principal Investigator (PI)* *-Sub-Investigator (Sub-PI)* *-Coordinator* *-Nurses* *-Pharmacists* **Give details in remarks Section*				*Research nurse and pharmacist were available*
Are CVs available for Key staff members (PI, Sub-PI, Coordinator)				
iii Education and Training	***Yes***	***No***	***NA***	***Observation / Recommendations***
Have CTS personnel received or are scheduled to receive any of following trainings? *o GCP* *o Trial related* *o Safety reporting* *o Pharmacovigilance Training* *o Other*				
Are training records available for study related staff?		✓		

Security and confidentiality is adequate to prevent unauthorized access to records?	✓			
Is there sufficient space to store materials, archive records, equipment to function properly?	✓			
Are generators and/or UPS available utilized at the facility?	✓			
iv. Safety	***Yes***	***No***	***NA***	***Observation / Recommendations***
Is there a system in place for personnel to report any safety concern or incidents?		✓		
v. Data Handling procedures and Computer Validation	***Yes***	***No***	***NA***	***Observation / Recommendations***
Does the CTS have adequate IT facilities e.g. Computers, internet available?	✓			
Is access to computers limited by an individual username and password system (Clinical Research team members cannot share a user name)?		✓		
vi. Records and Reports	***Yes***	***No***	***NA***	
Is there space available for document storage?	✓			
If yes, do access control systems to the area exist and are functional?	✓			
Is there a SOP or a system for the retention, storage, and destruction of records?		✓		
How does the site ensure the Sponsor's proprietary information is not disclosed to unauthorized personnel or external organizations?	✓			
vii. Records Retention and Archival	***Yes***	***No***	***NA***	***Observation / Recommendations***
Is there a dedicated facility/area for the archival of records?	✓			
Is there control access to the archival facility?	✓			
Is the environment of the facility monitored and controlled?	✓			
Is the retention time for records agreed with the sponsors?	✓			
Is there a method of electronic data archive (if required)?		✓		

Remarks of inspection team:

The panel observed that a common lift and passage was available for the O.T which was located on the same floor where CTS was located. It was opined that this can pose a potential risk to the GCP at the proposed site for clinical trials, therefore the panel unanimously recommended to defer the site for further improvements in site's layout and operations.

Concluding status of inspection / application :(Circle One)

Recommended for approval ☐
Deferred for improvements ☑
Recommended for rejection ☐

Name *Signature*

Inspector: *Dr. Faiza Bashir* *Signed*
Inspector: *Malik Muhammad Asad* *Signed*
Inspector: *Shafqat Hussain Danish* *Signed*

6. The case was placed before the CSC for consideration.

Decision:

The CSC keeping in view the recommendations of the inspection panel deferred the CTS Phase III & IV located at M/s Premium Medical Complex, Rawalpindi for further improvements in layout i.e. provision of dedicated/controlled entry/exit to the CTS.

7. The applicant has submitted CAPA vide letter dated 05th May 2025, fulfilling the requirements, relevant portion of reply is reproduced as under:

We are pleased to inform you that the recommended improvements to our designated clinical trial site have been duly implemented, and the floor has been dedicated exclusively for clinical trial operations. In this regard the revised layout plan is attached has Annexure-A for concentration

8. The case was placed before the CSC for consideration. The Committee decided the case as under:

Decision:

The CSC considered and approved the grant of license to act as Clinical Trial Site at M/s Premium Medical Complex, Rawalpindi for Phase III & IV Clinical Trials.

CASE No. 2.2:

APPLICATION FOR GRANT OF LICENSE TO ACT AS CONTRACT RESEARCH ORGANIZATION (CRO) FROM SCIENTIFIC RESEARCH SOLUTIONS. F. No. 15-82/2025-CRO (PS).

Application is received form Maj. Gen (R) Rehmat Khan, CEO Scientific Research Solutions Rawalpindi Pakistan having business address Al-Shifa Children Hospital, Al-Shifa Trust Eye Hospital, Jhelum Road Rawalpindi, Pakistan wherein request has been made for grant of license to act as CRO. The site has been granted license No. CTS 0044 to conduct Clinical Trails Phase II, III & IV. Ref. F. No. 15-17/2022.

02. The application is on Form-I of the Bio-Study Rules 2017 with prescribed fee of Rs. 370,030/- submitted vide slip number 03691551581 dated 03-02-2025.

03. After initial scrutiny of application in accordance with the pre- requisites as mentioned in Form-I of the Bio-Study Rules 2017, the following observations are made:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-III of The Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	Rs. 370,030/- submitted vide slip number 03691551581 dated 03-02-2025
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names	Attached

	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).	
4	Details of premises including layout plan of the site.	Attached
5	Details of the section wise equipment and machinery.	**Not provided.**
6	Names and qualifications of management.	Attached
7	Undertaking on stamp paper	**Not provided.**

04. Furthermore, to address the potential conflict of interest as the same site is also a licensed CTS, the applicant has submitted a declaration that:

> *"Al-Shifa Research Centre will neither participate in any clinical trial project in which the institute CRO (Scientific Research Solutions) is acting as Contract Research Organization (CRO), nor scientific research solutions will supervise any clinical trial project that is to be conducted by Al-Shifa Research Centre. This decision has been made to avoid any potential conflict of interest and to uphold the integrity and transparency of institute research activities."*

05. Accordingly, the Chairman CSC constituted following panel for inspection on 21st February, 2025:

a. Mr. Malik Muhammad Asad, Pharmacy Services Division, DRAP, Islamabad.
b. Mr. Shafqat Hussain Danish, Pharmacy Services Division, DRAP, Islamabad

06. The nominated conducted inspection of the proposed site on 26th February, 2025 and shared reports. Inspection panel reports are reproduced as under:

CONTRACT RESEARCH ORGANIZATION INSPECTION CHECKLIST

Name of facility: ***Scientific Research Solutions (CRO)***
Address: Al- Shifa Eye Trust Hospital, Jehlum Road Rawalpindi.
Organization Type: - Public ■ ***Not for Profit*** ☐ *Private* ☐ *Other-*
Name of Owner / Proprietor ***Maj. Gen. (R) Rehmat Khan***
Date of inspection: ***26/02/2025***

i. Organization and personnel	***Yes***	***No***	***NA***	***Observations / Recommendations***
Organizational chart exists and accurately represents the organization? *The following departments are needed:* • *Clinical Operations* • *Regulatory* • *IT* *Support Departments* • *HR* • *Finance* • *QC*	✓			
Are Job Descriptions Available for all personnel?	✓			
Are training records Available?	✓			
Are there personnel curricula (training, matrix / plan) established and	✓			

documented for each individual?				
Does the training program include new hire training 'and re-qualification training for personnel?		✓		
Has personnel been Appropriately trained to perform functions required by job descriptions?	✓			
Is there a procedure to assess and document personnel competency on an annual basis?	✓			
Have personnel received regulatory training? *GCP* ☑ *Others:* ***Research Methodology*** ***A I in Research*** ***Protocol Writing etc.***	✓			
Is there a system in place for personnel to report any safety concerns or incidents?	✓			
Are external contractors/vendors utilized? Are they qualified/ approved for use? *Is there an SOP that outlines this process?*	✓			
Is there a Quality Assurance Unit?		✓		
If yes, what are the roles of the Quality Control and the Quality Assurance group?		✓		
Does the Quality Assurance Unit perform audits, trend metrics and report the results to the Senior Management?		✓		
Is the Quality Assurance Unit independent from the personnel engaged in the direction or conduct of a clinical trial?		✓		*Yes, SOP Document 8*
ii. Standard Operating Procedures / Methods	***Yes***	***No***	***NA***	***Observations / Recommendations***
Is there a governing SOP that outlines the creation, revision, approval, distribution, document control and retirement of SOPs?	✓			
Is there a current index listing of the SOPs available?	✓			
Is there a schedule for review of the SOPs?	✓			
Are the SOPs in locations where they are used?		✓		
Is there a system for documenting and handling SOP/method deviations and CAPAs?		✓		
Is there a change control system for SOP/Methods?	✓			
Does the Organization have SOPs to cover all the aspects of clinical Operations e.g., Study start up, Study Conduct and Study Closeout/Completion?	✓			
iii. Facility	***Yes***	***No***	***NA***	***Observations / Recommendations***
Is security and Confidentiality adequate so as to prevent unauthorized access to records?	✓			
Is there sufficient space to store materials, archive records and for equipment to function properly?	✓			
Is the facility reasonably maintained and clean?	✓			
Is safety equipment (e.g. fire extinguishers etc.) available?	✓			

If yes, is the equipment maintained?	✓			
Does the Organization have a disaster recovery plan that covers all areas of the facility including computer systems and equipment?	✓			
Are generators utilized at the facility?	✓			
iv. Data handling Procedures and Computer Validation	***Yes***	***No***	***NA***	***Observations / Recommendations***
Is access to computers limited by an individual username and password system (Organization members cannot share a username)?	✓			
How is the computed network arid-- computer systems maintained, if applicable?	✓			
Are there a computer validation master plan and/or SOPs?		✓		
List computers systems and software utilized. Validated?		✓		
Are changes to computer systems controlled and documented?		✓		
Are records of computer system errors maintained and investigated?		✓		
Are records of hardware maintenance and repairs maintained?			✓	
Are computers backed up routinely to prevent loss of data? Is there a backup log?			✓	
Is there a preventative maintenance program for computer systems?			✓	
vii. Records and Reports	***Yes***	***No***	***NA***	***Observations / Recommendations***
Does a documentation control system exist and is functional?	✓			
Is there a SOP or a system for the retention, storage, and destruction of records?	✓			
How does the site ensure the sponsor's proprietary information is not disclosed to unauthorized personnel or external organizations?	✓			
viii. Record Retention and Archival	***Yes***	***No***	***NA***	***Observations / Recommendations***
Is there a dedicated facility/area for the archival of records?	✓			
Is there controlled access to the archival facility?		✓		
Is the environment of the facility monitored and controlled?	✓			
Is the procedure for archiving records outlined in an SOP?			✓	
Is the retention time for records stated in the SOP?		✓		
Is there a method of electronic data archival?		✓		
ix. Clinical Study Site *(IRB/IEC approval is necessary for conducting the clinical trial at a site. If local IRB/IEC is not available NBEC approval shall cover the site)*	***Yes***	***No***	***NA***	***Observations / Recommendations***
Does the facility have an IRB/IEC available?				

Remarks of inspection team:

The panel observed that Scientific Research Solutions being an independent entity has submitted Al-Shifa Eyes Trust's documents as their legal status along with the declaration of conflict of interest (for being CTS at the same time). Therefore, it was advised to provide legal documents for the CRO (as a separate entity). Furthermore, there was some civil work being carried out at the site, therefore the site is deferred for provision of required documents and completion of civil work.

Concluding status of inspection / application :(Circle One)

Recommended for approval	☐
Deferred for improvements	☑
Recommended for rejection	☐

Name	**Signature**
Inspector: Malik Muhammad Asad	Signed
Inspector: Shafqat Hussain Danish	Signed

07. Submitted for consideration and decision of the CSC, please.

Decision: The CSC after deliberation and on the recommendation of the inspection report, decided to defer the case for further improvements as highlighted in the inspection report.

08. Accordingly, shortcomings were shared through letter No. 16-55/2025-CSC, dated 07th March 2025. Applicant replied vide letter dated 07/05/2025 and submitted the Certificate of incorporation by SECP bearing number 0287303 "*Scientific Research Solutions (Pvt.) Ltd.*"

09. It is observed that the applicant in this case, Maj. Gen. (R) Rehmat Khan is also the license holder for CTS-0044 (w.e.f. 16th February 2024) which is a conflict of interest.

10. The case was placed before the Committee for consideration.

11. **Proceedings:**

During discussion it transpired that M/s Scientific Research Solution (CRO), Rawalpindi is operating in the premises of Al-Shifa Eye Trust Hospital, Rawalpindi, which is also an approved Clinical Trial Site (ASRC) license was granted to (Mr.) who is also the applicant in the instant application, and it prima-fascia is a Conflict of Interest. It was further deliberated that, during inspection of the site the applicant was advised to register the CRO as an independent entity.

The has applicant presented certificate of incorporation from SECP, wherein, M/s Scientific Research Solution is listed as a private limited company. However, the Form-I mentions Maj. Gen. (R) Rehmat Khan as the CEO Director and subscriber.

Decision:

The CSC considered and deferred the case for resolution of potential conflict of interest (in the ownership/ proprietorship of Al-Shifa Research Centre and proposed CRO, Scientific Research Solutions) and submission of revised documents accordingly.

CASE No. 2.3:

APPLICATION FOR LICENSE TO ACT AS CLINICAL TRIAL SITE FROM CENTRAL PARK TEACHING HOSPITAL, LAHORE. F.No.15-12/2022-CTS (PS)

Dr. Muhammad Ahmed, Director Clinical Trial Unit, Central Park Teaching Hospital, Lahore has applied for of license to act as Clinical Trial Site for phase II. The application is on Form-I of the Bio-Study Rules 2017 with fee of Rs. 100,000/- submitted vide slip No.091527953453.

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	Rs. 100,000/- submitted vide slip No.091527953453 dated *Nil.*
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).	Resolution of Board of Directors of Health and Education Foundation, SECP Certificate of Incorporation, SECP licence and Memorandum of Association attached. Punjab Healthcare Commission Registration Certificate 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.	Equipment list of CTU- Central Park Teaching Hospital attached.
6	Names and CVs of staff working in above sections.	Names and CVs of Clinical Trial Team attached.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Waste Management Agreement and department of Accident and Emergency attached.
8	Undertaking on stamp paper	Attached.

3. Previously application for phase II was submitted by the applicant and panel was constituted vide this office letter F.No.15-12/2022 DD (PS) dated 18th October 2022. The panel visited the premises and recommended to reject the application but the report and any CSC decision is missing in the file. The applicant has submitted the fresh application again. All relevant documents are attached. Applicant has submitted that PK/PD Lab analysis will be done by the central labs by the sponsor.

4. The following panel was constituted by the Chairman CSC for inspection of the site:
   i. Dr. Jaida Manzoor Consultant Paediatric Endocrinologist, Chair /Head of Department Paediatric Endocrinology CH. UCHS, Lahore
   ii. Mr. Faisal Shehzad, Additional Director DRAP Lahore.
   iii. Mr. Hafiz Muhammad Umair, Deputy Director (CTS-I), DRAP, Islamabad.

5. The panel inspected the CTS and submitted the report which is reproduced as under: -

Name of facility: M/s Central Park Teaching Hospital
Address: 31Km Ferozepur Road, Kahna Nou, Lahore.
Organization Type: Public ☐ Not for Profit ✓ Private ☐ Other-
Name of Owner / Proprietor: Mr. Tahir Javed, Mr. Riaz Ahmad Chohan
Date of inspection: 16-10-2024

i. General Information	Yes	No	NA	Observations / Recommendations
Is this CTS a primary care, secondary care or tertiary care facility? (Record one in observations section)	✓			Tertiary Care Facility
Is this the Composite CTS (Where Principal investigator is located)?	✓			
Is the facility registered with the Healthcare Commission?	✓			
If yes, is the certificate, available for review and is valid?	✓			PHCC Reg. No.-R-21494
Is there enough space available for proper functioning for clinical trials?		✓		Existing facility is only sufficient for recruitment/enrolment of subjects, investigational product administration, sample taking and record keeping for Phase-II clinical trial. Space for trial subjects (retention) needs to be established/allocated.
Is there an outpatient facility?	✓			
If yes, On an average how many patients visit per day?	✓			Approx. 200-250
Is there an inpatient facility?	✓			
If yes, how many beds?	✓			600 Beds
Have any clinical trials been conducted at this CTS in the past?		✓		New facility, no Phase-II clinical trial has yet been conducted. CTU is already approved for conducting Phase-III clinical trials.
If yes, how many clinical trials were conducted? Give details of the PI as well as nature and duration of the clinical trials.		✓		CTU @ Central Park hospital has completed 4 Phase-III clinical trial studies.
How many other studies currently ongoing at the site? If yes, how many clinical trials were conducted? Give details of the PI as well as nature and duration of the clinical trials.		✓		Currently, following Phase-III clinical trial studies are ongoing: 1. **YS-002** (A Phase III, Randomized, Comparator-Controlled, Double-Blind, Multicenter Study to Evaluate the Immunogenicity, Safety and Lot to Lot Consistency of Three Lots of a PIKA Rabies Vaccine (Vero Cell) for Human Use, Freeze-dried in Healthy Adults using a Post-Exposure Prophylaxis schedule) - Follow-up Stage 2. **V201_03** (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.) - Follow-up Stage. 3. **LVRNA021-III-01** (A Multi-center, Randomized, Blinded, Placebo controlled, Phase 3 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) - Close-out Stage 4. **ALVOTECII AVT06-GL-C01** (A Randomized, Double-masked, Parallel-group, Multicenter Clinical Study to Evaluate the Efficacy and Safety of AVT06 Compared with EU-Eylea® in Subjects with Neovascular (wet) Age-related Macular Degeneration) - Close-out Stage
Is there a pharmacy / dedicated investigational Medicine dispensing area?	✓			Improvements were suggested in this regard: 1. Comprehensive Record Keeping 2. Inventory Management Systems 3. Proper Temperature and Humidity Control 4. Security and Access Control 5. Documentation and Record Keeping 6. Adherence Monitoring 7. Labeling and Identification 8. Segregation of Products 9. Expiry and Disposal Procedures 10. Clean room and Biosafety cabinet for dilutions etc. for investigational products.
If yes, does the CTS have required storage facility for routine operations?	✓			Following were the observations and improvements were suggested in this regard: 1. No safety alarm system was in place. 2. Lack of air conditioning or environmental control system. 3. IT facilities, archiving room and other emergency arrangements were not operational. 4. Biosafety cabinet was not functional; area was not controlled/Clean room was not maintained with respect to handling of blood samples of subjects. 5. Equipment calibration record was not available and log books were not maintained.
If yes, does the CTS have required trial related Investigational Product storing facility? (Investigational Product Provided by the sponsor as per requirements of the protocol).	✓			Continuous monitoring of temperature and humidity is essential, with proper record for monitoring any deviations.

Does the CTS have Laboratory services?		✓		Protocol related laboratory services shall be outsourced (local/foreign) as agreed with sponsor.
If yes, is in-house or central?		✓		
Is there an X-Ray facility?	✓			
If yes, is it on-house or central?	✓			Central.
Does the facility have an incinerator? If yes, document the average weight of Hospital waste disposed of per month.		✓		
If No, does the facility, have a contract with a Hospital waste management Company?	✓			They have an MoU with third party vendor AT waste management
ii. Study Related Staff	**Yes**	**No**	**NA**	**Observations / Recommendations**
Does the CTS have, any of the study related personnel on staff? -Principal Investigator (PI) -Sub-Investigator (Sub-PI) -Coordinator -Nurses -Pharmacists *Give details in remarks Section	✓			Dr. Muhammad Ahmad, Director (CTU) Dr. Ibrahim Siddiqui, Assistant Director (CTU) Dr. Muhammad Zafran (Investigator) Dr. Fatima Rasheed (Investigator) Dr. Shazia Shakeel (Investigator) Mr. Hamza Mahmood (Pharmacist) Mr. Shazaib (Pharmacist) Mayeda Aslam (Lab Technician) Ezaz Almas (Nurse/Phlebotomist)
Are CVs available for Key staff members (PI, Sub-PI, Coordinator)	✓			
iii Education and Training	**Yes**	**No**	**NA**	**Observation / Recommendations**
Have CTS personnel received or are scheduled to receive any of following trainings? o GCP o Trial related o Safety reporting o Pharmacovigilance Training o Other		✓		CTS personnel should be trained in critical areas such as GCP, trial-related procedures, safety reporting, and pharmacovigilance.
Are training records available for study related staff?		✓		No record of trainings for CTU staff on updated Good Clinical Practices (GCP), GDP & equipment usage was available.
Security and confidentiality is adequate to prevent unauthorized access to records?		✓		New site, SOPs for the purpose need to be developed and implemented.
Is there sufficient space to store materials, archive records, equipment to function properly?	✓			However, SOPs needs to be well defined and keep the manual record more securely.
Are generators and/or UPS available utilized at the facility?	✓			Clinical Trial site will be provided with energy backup from hospital.
iv. Safety	**Yes**	**No**	**NA**	**Observation / Recommendations**
Is there a system in place for personnel to report any safety concern or incidents?		✓		SOPs for the purpose need to be developed and implemented.
v. Data Handling procedures and Computer Validation	**Yes**	**No**	**NA**	**Observation / Recommendations**

Does the CTS have adequate IT facilities e.g. Computers, internet available?	✓			Backup Data preservation and its integrity must be included in SOPs.
Is access to computers limited by an individual username and password system (Clinical Research team members cannot share a user name)?		✓		There is no system for electronic database.
vi. Records and Reports	**Yes**	**No**	**NA**	**Observation / Recommendations**
Is there space available for document storage?	✓			
If yes, do access control systems to the area exist and are functional?		✓		Facility is almost developed, however, some minor points are required to be addressed w.r.t. fixtures and security.
Is there a SOP or a system for the retention, storage, and destruction of records?	✓			
How does the site ensure the Sponsor's proprietary information is not disclosed to unauthorized personnel or external organizations?		✓		The panel suggested to ensure non-disclosure of information to unauthorized personnel by implementing following practices: 1. Confidentiality Agreements 2. Data Access Control 3. Physical Security Measures 4. Data Sharing Controls 5. Monitoring and Audits
vii. Records Retention and Archival	**Yes**	**No**	**NA**	**Observation / Recommendations**
Is there a dedicated facility/area for the archival of records?	✓			
Is there control access to the archival facility?		✓		Facility is almost developed, however, some minor points are required to be addressed w.r.t. fixtures and security.
Is the environment of the facility monitored and controlled?		✓		Air conditioners are yet to be installed.
Is the retention time for records agreed with the sponsors?	✓			SOP is available. However, retention time for records is agreed with sponsor.
Is there a method of electronic data archive (if required)?		✓		The panel further advised to comply with Good Documentation Practices (GDP) i.e. to develop and implement standard operating procedures (SOPs) specifically tailored to documentation requirements for clinical trials, ensuring adherence to guidelines for record accuracy, completeness, traceability and data integrity during clinical trials.

Remarks of inspection team:

In compliance to letter bearing No. 15-12/2022-CTS(PS), dated 10th October 2024, nominated inspection panel, comprising of Dr. Jaida Manzoor (Consultant Pediatric Endocrinologist, Chair/Head of Department Pediatric Endocrinology Children Hospital, UCHS, Lahore), Mr. Faisal Shahzad (Additional Director, DRAP, Lahore), Mr. Hafiz Muhammad Umair (Deputy Director, CTS-I, Pharmacy Services Division-DRAP, Islamabad), visited the premises of M/s Central Park Teaching Hospital, 31Km Ferozepur Road, Kahna Nou, Lahore, on 16th October 2024.

The inspection was focused on the Clinical Trial Unit (CTU) and associated facilities. The inspection team conducted a thorough assessment of M/s Central Park Teaching Hospital's Clinical Trial Unit (CTU). The key areas covered included the reception/waiting area, screening and consent rooms,

Research Pharmacy, IMP administration area, and emergency handling services, along with IT facilities and archiving rooms. Further, the panel reviewed hospital-related legal documents, PHCC registration, SECP registration, Standard Operating Procedures (SOPs), and Job Descriptions (JDs) of CTU staff. The panel noted gaps/ shortcomings and discussed improvements in light of above given checklist with respect to clinical trial-related activities.

Keeping in view the infrastructure, staff experience, qualifications, documentation, and other facilities available at the CTU, the panel recommends to defer the request of M/s Central Park Teaching Hospital, Lahore for Phase II clinical trials (except their PK/PD parts which will be responsibility of the Sponsor) and provide sufficient time to CTU management team for necessary improvements of their facility as per the checklist i.e. to develop and implement a detailed facility improvement plan, ensuring all critical areas such as safety systems, environmental controls, and laboratory standards are met.

Concluding status of inspection / application :(Circle One)

Recommended for approval	☐
Deferred for improvements	☑
Recommended for rejection	☐

	Name
Inspector:	Dr. Jaida Manzoor
Inspector:	Mr. Faisal Shahzad
Inspector:	Hafiz Muhammad Umair

6. The case was placed before the Committee for consideration.

Decision:

The CSC after deliberation and on recommendation of panel of experts, decided to defer the case for further improvements and fulfilment of shortcomings noted in its inspection report dated 16th October, 2024.

7. The shortcomings were communicated vide this office letter F.No.16-51/2024 dated 31.10.2024. The applicant responded to the afore mentioned letter and submitted the CAPA vide letter dated 27th March, 2025 fulfilling the shortcomings following which a panel of inspectors was constituted by the Chairman CSC on 22/04/2025 which was then re-constituted on 13/05/2025.

8. The nominated panel inspected the premises on 16.05.2025 and submitted the report. Remarks of the inspection panel are reproduced as under: -

Remarks of inspection team:

The site is having dedicated pharmacy for the storage of IMPs. SOPs and training record of the CTS staff was also available. The panel suggested some improvements in the area designated for transfer of trail subjects in case of emergency. The site is recommended to act as CTS Phase III and IV clinical trials and Phase –II Clinical trials except their PK/PD part which will be performed by the sponsor (subject to GCP inspection before every Phase-II clinical trial).

9. Another application (F. No. 15-12/2021 - CTS) from Dr. Muhammad Ahmed, CNIC No. 31304-4798820-7, Director Clinical Trial Unit, Central Park Teaching Hospital, Lahore for renewal of license (CTS-0049) to act as Clinical Trial Site for phase III & IV is also under process where application on Form-III of the Bio-Study Rules 2017 along with fee of Rs. 100,000/- submitted vide slip No.819220390 was received by this office on 19th March, 2024.

10. The shortcomings were communicated vide this office letter F.No.15-12/2021-CTS dated 26.04.2024. The applicant responded to the afore mentioned letter and submitted the CAPA vide letter dated 15th May, 2024 fulfilling the shortcomings following which a panel of inspectors was constituted by the Chairman CSC on 07/06/2024 which was then re-constituted on 07/10/2024.

11. The inspection report in the subject case was not received by this office, therefore the Chairman CSC mandated the same panel as constituted for F. No. 15-12/2022 - CTS to inspect the site for renewal of license to act as Phase-III-IV clinical trial site.

12. The case was placed before the CSC for consideration.

Decision:

The CSC considered and approved the grant of license to act as Clinical Trial Site at M/s Central Park Teaching Hospital (Clinical Trial Unit), Lahore, for Phase III and IV clinical trials and Phase –II Clinical trials except their PK/PD part which will be performed by the sponsor (subject to GCP inspection before every Phase-II clinical trial)

CASE No. 2.4:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL SITE PHASE III- IV FROM REHMATUL LIL ALAMEEN POSTGRADUATE INSTITUTE OF CARDIOLOGY LAHORE. F. NO.15-81/2025-CTS (PS).

Dr. Farid Ahmad Chaudhary Medical Superintendent Rehmatul Lil Alameen Postgraduate Institute of Cardiology Lahore, has applied vide letter dated 13/01/2025, wherein request has been made for approval/registration of subject clinical trial site for Phase III and IV. The application is submitted on prescribed Form-I of the Bio-Study Rules 2017. Fee of Rs. 125,030/- has been deposited vide challan No.01166401440, dated 23/01/2025.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of the Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	Rs. 125,030/- has been deposited vide challan No.01166401440, dated 23/01/2025.
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 Rehmatul-lil-Alameen Post-Graduate Institute of Cardiology (RAIC), PESSI, Multan Road Lahore is a 50-beded Post-Graduate Teaching Cardiac Institute, owned by Punjab Employees Social Security Institution (autonomous body under Labour department, Government of Punjab) having Cardiology (including interventional cardiology) and Cardiac Surgery Departments, with provision of Free State of the art Cardiac facilities to PESSI (Punjab Employees Social Security Institution) Secured workers and their families and to the general public.
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 **List of machinery/ equipment required for clinical trials to be carried out at the proposed site is required.**
6	Names and qualifications of the management.	List of hospital staff is attached **CVs along with organogram and**

		details of staff for the CTS is required.
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	Attached **Documents(SOPs) for the utilization of allied facilities for trial subjects (in case of SAEs) and their scope for the purpose of research need to be provided.**
8	Undertaking on stamp paper	Attached

3. The Chairman CSC constituted a panel of inspectors on vide letter dated F. No. 15-81/2025 dated 19.02.2025, the premises was inspected by two members of the nominated panel on 16.05.2025 and remarks of the panel are reproduced as under: -

Remarks of inspection team: -

Reference to the letter No. 15-81/2025 dated 19.02.2025 the nominated panel visited the site on 16.05.2025. The panel advised improvements in different areas of the CTS as the site is not fulfilling the criteria (GCP compliance) as outlined in the inspection checklist. The site is therefore deferred for improvements.

4. The case was placed before the CSC for consideration.

Decision:

The CSC on the recommendation of the inspection panel deferred the case for improvements as highlighted in the inspection checklist.

CASE No. 2.5:

APPLICATION FOR RENEWAL OF CLINICAL TRIAL SITE PHASE III- IV FROM MEDICARE HOSPITAL RAWALPINDI. F. NO.15-39/2021-CTS (PS).

Prof. Rizwana Chaudhri, CEO Medicare Hospital Rawalpindi submitted an application wherein request has been made for renewal of subject clinical trial site for Phase III and IV. The site was granted license to act as CTS Phase III & IV on 28-10-2021 (CTS0076). The application is submitted on prescribed Form-III of the Bio-Study Rules 2017. Fee of Rs. 125,030/- has been deposited vide challan No.69259571693, dated 08/10/2024.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of the Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	Rs. 125,030/- has been deposited vide challan No.69259571693, dated 08/10/2024.
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).	**Required** (The applicant in her previous application has stated that the hospital is single owner proprietorship, however proof of ownership/land documents/ lease agreement and NTN certificate are not 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 management.	Attached
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	**Documents(SOPs) for the utilization of allied facilities for trial subjects (in case of SAEs) and their scope for the purpose of research need to be provided.**
8	Undertaking on stamp paper	Attached.

3. The Chairman CSC constituted a panel of inspectors on vide letter dated F. No. 15-39/2021 dated 19.02.2025, the premises was inspected by the nominated panel on 16.05.2025 and remarks of the panel are reproduced as under: -

Remarks of inspection team: -

The panel recommends renewal of license to act as Phase –III (trial specific) clinical trial site exclusively for I'm women study/trial.

4. The case was placed before the CSC for consideration.

Decision:

The CSC considered and approved the grant of license to M/s Medicare Hospital Rawalpindi to act as Phase –III (trial specific) clinical trial site exclusively for I'm women study/trial.

CASE No. 2.6:

APPLICATION FOR LICENSE TO ACT AS CLINICAL TRIALS SITE FOR PHASE I & PHASE II STUDIES BY CHUGHTAI LABORATORY, LAHORE, F.No.15-04/2022-CTS

Application was received from Dr. Omer Rasheed Chughtai Director Operations of M/s Chughtai Lab, 7-Jail Road Lahore, wherein he has applied to for grant of license to act as Clinical Trial Site Phase I-II. Previously license to act as Clinical Trial Site Phase III –IV (CTS 0051) was issued on 18.03.2021 which has expired on 17.3.2024. This is a fresh application is on Form-I of the Bio-Study Rules 2017 along with fee of Rs. 125,000/- deposited vide slip no. 5016551927 dated 10th September, 2024.

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules 2017.	Applicant has applied for renewal of license (BAL-0002) for BA/BE Lab at the same premises.
2	Prescribed processing fee	Rs. 125,000/- deposited vide slip no. 5016551927

		dated 10th September, 2024.
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 (Incorporated as diagnostic laboratory by SECP)
4	Details of premises including layout plan of the site.	**Required** **(Layout plan of the different floors of laboratory are provided, however a clear layout plan for CTS is required)**
5	Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.	**Details of machines with respect to their bio-analytical application in clinical trials is required.**
6	Names and qualifications of the management.	**List of qualified technical personnel along with organogram is required.**
7	Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.	**SOP for Emergency Medical Services not attached.**
8	Undertaking on stamp paper	Attached.

3. In view of the above the proposals are submitted for kind consideration:
   a) The applicant may be advised to rectify shortcomings.
   b) Meanwhile, a panel of experts may also be constituted for inspection of the proposed CTS

4. Accordingly, after communication of shortcomings, the Chairman CSC constituted following panel for inspection:
   i. Mr. Nadeem Irfan Bukhari
   ii. Mr. Faisal Shehzad
   Mr. Hafiz M. Umair
   iii. Mr. Zain Ul Abideen

5. The panel visited the facility on 16th May 2025 and submitted inspection report with following remarks:

Remarks of inspection team: -

The panel after inspection was of the opinion that the application to act as Phase-I & II CTS at Chughtai Lab, Lahore may be rejected due to unavailability of Clinical Trial Site related facilities as per prescribed checklist.

6. The case was placed before the CSC for consideration.

Decision:

The CSC on the recommendation of inspection panel considered and rejected the application of M/s Chughtai Lab, 7-Jail Road Lahore to act as Phase –I & II clinical trial site due to non-availability of CTS facility as per prescribed checklist.

CASE No. 2.7:

APPLICATION FOR GRANT OF LICENSE TO ACT AS CONTRACT RESEARCH ORGANIZATION (CRO) FROM KINGSBRIDGE BIOSCIENCES. F. No. 15-90/2025 (CRO)).

Application is received form Anayat Rasool, CEO M/s Kingsbridge Biosciences (Pvt.) Ltd Islamabad business address Basement Plaza No. 19 Commercial 1 Naval Anchorage Islamabad wherein request has been made for grant of license to act as CRO.

2. The application is on Form-I of the Bio-Study Rules 2017 with prescribed fee of Rs. 370,030/- submitted vide slip number 505090398854 dated 25-02-2025.

3. After initial scrutiny of application in accordance with the pre- requisites as mentioned in Form-I of the Bio-Study Rules 2017, the following observations are made:

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-III of The Bio-Study Rules 2017.	Attached
2	Prescribed processing fee	Rs. 370,030/- submitted vide slip number 505090398854 dated 25-02-2025.
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.	Attached
6	Names and qualifications of management.	Attached
7	Undertaking on stamp paper	Attached

4. In view of the above it is proposed that a panel of experts may be constituted for the inspection of the proposed premises for the grant of license to act as CRO, if agreed, please.

5. The Chairman CSC constituted following panel for inspection:
   i. Malik Muhammad Asad, Secretary/Deputy Director-PS-DRAP.
   ii. Shafqat Hussain Danish, Deputy Director-PS-DRAP

6. The nominated panel visited the facility on 17th May 2025 and submitted inspection report with following remarks:

Remarks of inspection team: -

The panel after inspection was in opinion that the CRO layout need to be revised as per minimum division required to perform activities, QMS section and SOPs need to be developed with other required/related facilities as per prescribed checklist and the CRO may be deferred for improvement.

7. The case was placed before the CSC for consideration.

Decision:

The CSC considering the inspection report deferred the application of M/s Kingsbridge Biosciences (Pvt.) Ltd Islamabad to act as CRO for improvements as highlighted in the inspection report.

CASE No. 2.8:

APPLICATION TO ACT AS CLINICAL TRIAL SITE FROM M/S AGA KHAN UNIVERSITY MATIARI RESEARCH & TRAINING CENTER, MATIARI TO ACT AS CLINICAL: TRIAL SITE FOR PHASE-II CLINICAL TRIAL TITLED, "ABILITY OF THE VE818 TO REDUCE ENTEROPATHOGEN COLONIZATION AND IMPROVE ENVIRONMENTAL ENTEROPATHY IN PREGNANT WOMEN: A PROOF OF CONCEPT AND PHASE II RANDOMIZED PLACEBO-CONTROLLED TRIAL IN BANGLADESH, PAKISTAN, ZAMBIA AND BURKINA FASO". F. No.15-78/2025-CTS (PS).

Application was received from Prof. Dr. Zulfiqar Bhutta, Professor & Founding Director, Institute of Global Health & Development, Aga Khan University Karachi, for approval of M/s Aga Khan University Matiari Research & Training Center, Matiari for Phase-II Clinical Trial titled, "Ability of the VE818 to Reduce Enteropathogen Colonization and Improve Environmental Enteropathy in Pregnant Women: a proof of concept and Phase-II Randomized Placebo-Controlled trial in Bangladesh, Pakistan, Zambia and Burkina Faso", the application is on prescribed Form-I of the Bio-Study Rules, 2017, along with prescribed processing fee of Rs. 150,000/- deposited vide challan No. 716453966275, dated 05th September, 2024 (for renewal of the site).

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

S. No.	Required Documents / Information	Remarks
1	Application on prescribed Form-I of The Bio-Study Rules, 2017.	Attached
2	Prescribed Fee	Rs. 150,000/- deposited vide challan No. 716453966275, dated 05th September, 2024 (for renewal of the site). * Revised challan required for new application need to be provided.
3	Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).	The Aga Khan University Order 1983 is attached. Certificate issued by Sindh Healthcare Commission need to be provided.
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 list of equipment is not fulfilling Phase-I/II clinical trials requirements. (Trial design may be reviewed and may be inspected by the panel)
6	Names and qualifications of the above sections along with their staff.	CVs of staff is attached but details regarding on-site PI are not provided.
7	Details of the allied facilities associated with the	Instead of details for available facilities at

	trial center including ambulatory services, emergency handling etc.	applied site a letter regarding Collaboration Between AKU Research & Training Center, Matiari, and Aga Khan Maternal and Child Care Center (AKMCC), Hyderabad is attached.
8	Undertaking on stamp paper.	Attached

3. After initial scrutiny following shortcoming observed:

i. Details regarding Site in-charge need to be provided, as Prof. Dr. Zulfiqar Bhutta and Prof. Dr. Asad Ali and Certificate issued by Sindh Healthcare Commission needs to be provided.
ii. Original challan (DRAP Copy) need to be provided.
iii. Instead of details regarding available facilities at applied site a letter regarding Collaboration Between AKU Research & Training Center, Matiari, and Aga Khan Maternal and Child Care Center (AKMCC), Hyderabad is attached.
iv. Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. need to be provided.

4. Accordingly, the Chairman CSC constituted following panel for inspection of the applied site and approved the shortcomings:

i. Prof. Mirza Tasawer Baig
ii. Director PS
iii. Mr. Abdul Rasool Shaikh, please.

5. Accordingly, inspection letter communicated on 21st February 2025 and shortcomings were issued on 27th March 2025.

6. Reply was received from Prof. Dr. Zulfiqar Bhutta, Professor & Founding Director, Institute of Global Health & Development, Aga Khan University Karachi & Professor Dr. Syed Asad Ali Chair, Department of Community Health Sciences the Noordin Noormahomed Sheriff Endowed Chair Professor of Pediatrics & Community Health Sciences. Wherein, F.R. is submitted in reference to this Division letter even No. dated 27th March 2025. Applicant reply is reproduced as under:

Subject: *RESPONSE TO APPLICATION FOR APPROVAL OF M/S AGA KHAN UNIVERSITY MATIARI RESEARCH & TRAINING CENTER. MATIARI FOR PHASE-II CLINICAL TRIAL TITLED, "ABILITY OF THE VE818 TO REDUCE ENTEROPATHOGEN COLONIZATION AND IMPROVE ENVIRONMENTAL ENTEROPATHY IN PREGNANT WOMEN: A PROOF OF CONCEPT AND PHASE II RANDOMIZED PLACEBO-CONTROLLED TRIAL IN BANGLADESH, PAKISTAN, ZAMBIA AND BARKINA FASO". F. No. 15-78/2025-CTS (PS).*

Dear Sir/Madam,

Thank you for your letter, F. No. 15-78/2025-CTS (PS) dated 07th February in response to our application.

Your attention to this application is appreciated and below are the responses to the shortcomings communicated in that letter.

S. No.	***DRAP Comments***	***Response***
i.	*Details regarding the Site in charge need to be provided, as Prof. Dr. Zulfiqar Bhutta and Prof. Dr. Asad Ali and certificate issued by Sindh Healthcare Commission needs to be provided.*	*The CVs and PMC licenses of the following are attached in Annexure 1.1* *a. Dr. Zulfiqar Bhutta – Founder of Matiari Research & Training Center*

		b. Dr. Syed Asad Ali – Principal Investigator *c. Dr. Sheraz Ahmed – Senior Manager Site.* *The official clarification letter from Sindh Healthcare Commission (SHCC) is shared in Annexure 1.2. It clarifies that since Matiari Research & Training Center (MRTC) is a research facility and does not operate as a healthcare service provider for general public, hence SHCC registration and licensing process is not applicable on the services offered by MRTC.*
ii.	*Original challan (DRAP Copy) need to be provided.*	*The original challan copy has been provided to DRAP with the initial application in October 2023, so the copy of license challan and original fee adjustment challan copy are shared in Annexure 02.*
iii.	*Instead of details regarding available facilities at applied site a letter regarding Collaboration Between AKU Research & Training Center, Matiari, and Aga Khan Maternal and Child Care Center (AKMCC), Hyderabad is attached.*	*The details regarding the available facilities at the applied site are shared in Annexure 03*
iv.	*Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc. need to be provided.*	*The details of the allied facilities associated with the trial center, including ambulatory services, emergency handling etc. are shared in Annexure 04*

We appreciate your prompt attention to this matter and are available for any further information or clarification you may require.

Thank you for considering this application.

Sincerely,

7. In reference to inspection panel letter issued on 31st October 2024, the nominated panel member conducted inspection on 10th to 11th December 2024 and shared reports. Inspection panel reports are reproduced as under:

- ✓ **Panel report**

CLINICAL TRIAL SITE (CTS) INSPECTION CHECKLIST

Name of facility: **Matiari Research & Training Center**
Address: **Near National Highway, Matiari, Sindh**
Organization Type: - Public ☐ Not for Profit ■ Private ☐ Other-
Name of Owner / Proprietor: **Aga Khan University**
Date of inspection: **04-04-2025**

i. General Information	Yes	No	NA	Observations / Recommendations
Is this CTS a primary care, secondary care or tertiary care facility? (Record one in observations section)			✓	It is a purpose-built research facility.
Is this the Composite CTS (Where Principal investigator is located)?		✓		PI (Dr. Asad Ali) is located in Karachi. Sub-PI (Dr. Sheraz Ahmed) is located in Matiari.
Is the facility registered with the Healthcare Commission?			✓	The official clarification letter from Sindh Healthcare Commission (SHCC) is shared along. It clarifies that since Matiari Research & Training Center (MRTC) is a research facility and does not operate as a healthcare service provider for general public, hence SHCC registration and licensing process is not

				applicable on the services offered by MRTC.
If yes, is the certificate, available for review and is valid?			✓	
Is there enough space available for proper functioning 'for clinical trials?	✓			
Is there an outpatient facility?		✓		
If yes, On an average how many patients visit per day?			✓	
Is there an inpatient facility?		✓		
If yes, how many beds?			✓	
Have any clinical trials been conducted at this CTS in the past?	✓			
If yes, how many clinical trials were conducted? Give details of the PI as well as nature and duration of the clinical trials.				11 Clinical trials were conducted. Details are given in supporting documents.
How many other studies currently ongoing at the site? If yes, how many clinical trials were conducted? Give details of the PI as well as nature and duration of the clinical trials.				02 other studies are currently on-going. 11 clinical trials were conducted. Details are given in supporting documents.
Is there a pharmacy / dedicated investigational products dispensing area?	✓			
If yes, does the CTS have required storage facility for routine operations?	✓			
If yes, does the CTS have required trial related Investigational Product storing facility? (Investigational Product Provided by the sponsor as per requirements of the protocol).	✓			
Does the CTS have Laboratory services?	✓			
If yes, is in house or central?				In-house laboratory services of CTS are utilized for sample collection only and for some storage at -80. Central laboratory services of Aga Khan University are utilized for sample processing and analysis.
General Information	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there an X-Ray facility?		✓		
If yes, is it on-house or central?			✓	
Does the facility have an incinerator? If yes, document the average weight of Hospital waste disposed of per month.		✓		
If No, does the facility', have a contract with a Hospital waste management Company?	✓			CTS does not have an incinerator; however, these services are in contract with Aga Khan University.
ii. Study Related Staff	**Yes**	**No**	**NA**	**Observations/Recommendations**
Does the CTS have, any of the study related personnel on staff? -Principal Investigator (PI) -Sub-Investigator (Sub-PI) -Coordinator -Nurses -Pharmacists. *Give details in remarks Section	✓			CTS has all the study-related personnel listed below stationed on the facility of MRTC: **-Sub-Investigator-** Dr. Sheraz Ahmed **-Coordinator-**Dr. Fayaz Umrani **-Nurses-** Zubaida Zameer, GulBano Aijaz, Aisha Bano, Najma Talpur, Nazia Siyal **-Pharmacist-**Alisha Memon The **Principal Investigator** is Dr. Syed Asad Ali, stationed at Aga Khan University, Karachi.
Are CVs available for Key staff	✓			CVs are shared in supporting documents.

members (PI, Sub-PI, Coordinator)				
iii Education and Training	**Yes**	**No**	**NA**	**Observations/Recommendations**
Have CTS personnel received or are scheduled to receive any of following training? o GCP o Trial related o Safety reporting o Pharmacovigilance Training o Other	✓			GCP Trainings Trial related training Safety Reporting Pharmacovigilance Training
Are training records available for study related staff?	✓			Certificates and training records are shared.
Security and confidentiality is adequate to prevent unauthorized access to records?	✓			
Is there sufficient space to store materials, archive records, equipment to function properly?	✓			
Are generators and/or UPS available utilized at the facility?	✓			
iv. Safety	**Yes**	**No**	**NA**	**Observations / Recommendations**
Is there a system in place for personnel to report any safety concern or incidents?	✓			Yes, the SOP for safety reporting and pharmacovigilance is shared.
v. Data Handling procedures and Computer Validation	**Yes**	**No**	**NA**	**Observations / Recommendations**
Does the CTS have adequate IT facilities e.g. Computers, internet available?	✓			
Is access to computers limited by an individual username and password system (Clinical Research team members cannot share a user name)?	✓			
vi. Records and Reports	**Yes**	**No**	**NA**	**Observations / Recommendations**
Is there space available for document storage?	✓			
If yes, do access control systems to the area exist and are functional?	✓			
Is there a SOP or a system for the retention, storage, and destruction of records?	✓			SOPs are shared.
How does the site ensure the sponsor's proprietary information is not disclosed to unauthorized personnel or external organizations?	✓			The site protects sponsor-owned proprietary information by mandating institutionally approved confidentiality agreements for every study team member, restricting access to locked physical files and encrypted, password protected digital databases providing recurrent GCP-aligned data security training that emphasizes secure handling of sponsor materials. All communications are routed through the Principal Investigator or a designated coordinator. Additionally, whenever data must be shared beyond the institution, a Data Access Agreement (DAA) or Data Transfer Agreement (DTA) is executed in line with institutional policy and only after ERC and Research office approval, ensuring that no proprietary information is released to unauthorized individuals or external organizations.
vii. Records Retention and Archival	**Yes**	**No**	**NA**	**Observations/Recommendations**

Is there a dedicated facility/area for the archival of records?	✓			
Is there control access to the archival facility?	✓			
Is the environment of the facility monitored and controlled?	✓			
Is the retention time for records agreed with the sponsors?	✓			
Is there a method of electronic data archive (if required)?	✓			

Remarks of inspection team:

The panel recommends grant of license to act as trial specific clinical trial site subject to provision of registration from Sindh Healthcare Commission and approval of the study/trial.

Concluding status of inspection / application :(Circle One)

Recommended for approval/renewal.	☐
Deferred for improvements.	☑
Recommended for rejection.	☐

	Name	***Signature***
Inspector:	*Prof Dr. Mirza Tasawer Baig*	*Signed*
Inspector:	*Mr. Abdullah (Director-PS)*	*Signed*
Inspector:	*Mr. Abdul Rasool Sheikh*	*Signed*

8. The case was placed before the CSC in its 56th meeting held on 29th April 2025. The CSC decided the case as follows:

Decision:

The CSC keeping in view the recommendations of the inspection panel deferred M/s Aga Khan University, Matiari Research & Training Center, Matiari, Sindh to act a trial specific Clinical Trial Site for "*VE818 Clinical Trial*" for provision of license/registration from Sindh Healthcare Commission.

9. Accordingly, the CSC decision was communicated to the applicant vide letter bearing No. 16-56/2025-CSC, dated 06th May 2025.

10. The case was placed before the CSC for consideration.

Decision:

The CSC considered and deferred the case for submission of registration of the applied Clinical Trial Site (i.e. M/s Matiari Research & Training Center, Matiari) by Sindh Health Care Commission.

AGENDA ITEM 3: APPROVAL AND REGISTRATION OF CLINICAL TRIAL OR BA/BE STUDY

CASE No. 3.1:

APPLICATION FOR APPROVAL OF A CLINICAL TRIAL TITLED "A PHASE 2B RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TOBEVIBART+ELEBSIRAN COMBINATION THERAPY VERSUS BULEVIRTIDE IN PARTICIPANTS WITH CHRONIC HDV INFECTION (ECLIPSE 3) PROTOCOL NO.: VIR-CHDV-V206", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI, (ECLIPSE-3 Trial). F. NO.03-68/2025-CT (PS)

Application was received from Dr. Saeed Hamid, National-PI & Professor of Medicine Consultant Gastroenterologist Director, Clinical Trials Unit, Aga Khan University, Stadium Road, Karachi, received on 16th April 2025. The request has been made for approval of the subject clinical trial. Application is on prescribed Form-II, along with a fee of Rs. 245,000/- deposited vide challan No. 60813404502, dated 03rd April, 2025.

2. The application is reproduced as follows:

Re: Clinical Trial Application -Phase 3 Study

Protocol Title: A Phase 2b Randomized, Open-label Study to Evaluate the Efficacy and Safety of Tobevibart + Elebsiran Combination Therapy versus Bulevirtide in Participants with Chronic HDV Infection (ECLIPSE 3)
Protocol No.: VIR-CHDV-V206
Sponsor: Vir Biotechnology, Inc.
EU CT No.: 2024-520062-54-00

For and on behalf of the sponsor, Vir Biotechnology, Inc., we herewith submit a clinical trial application for the above-mentioned Phase 2b protocol.

This application concerns a Phase 2b study evaluating the efficacy and safety of tobevibart (VIR-3434) +elebsiran (VIR-2218) combination therapy compared with bulevirtide (BLV). The study will include adult participants ~ 18 to 70 years with chronic HDV infection on nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy active against HBV.
The primary efficacy endpoint for Part 1 is I-IDV RNA < LLOQ, TND at Week 48 in participants receiving tobevibart+elebsiran versus BLV. The primary endpoint for Part 2 is HDV RNA <LLOQ, TND 24 weeks after the interruption of tobevibart+elebsiran. Participants will be followed for 144 weeks following tobevibart+elebsiran interruption to assess the durability of SVR. The total study duration for each participant is planned to be up to 270 weeks.
The trial is prospective, multicenter, randomized, open-label study and will be executed in accordance with the protocol enclosed.

Background information
Hepatitis D virus (HDV) is a defective, hepatotropic pathogenic agent dependent on hepatitis B surface antigen (HBsAg) to complete its replication cycle and sustain infection. The global prevalence of HDV is estimated to be at least 12 million people worldwide.
Chronic HDV infection is the most aggressive form of viral hepatitis due to rapid progression to cirrhosis, liver failure, hepatocellular carcinoma (HCC), and death. Results from a recent meta-analysis examining the association between HDV RNA detectability, liver morbidity and mortality showed that persons with detectable HDV RNA were at higher risk of experiencing liver-related events, including developing cirrhosis, HCC and undergoing liver transplantation, and were at higher risk of mortality compared to those with undetectable HDV RNA.

Conversely, the loss of detectable HDV RNA is strongly associated with a lower likelihood to experience liver-related complications, and long-term suppression of HDV RNA is associated with more favourable clinical outcomes. HDV viral suppression is the most indicative surrogate marker for improved long-term clinical outcomes in patients with chronic HDV infection.

Available treatment options for HDV infection are limited to pegylated-interferon alpha (PEG-IFNα) and in some regions of the world, BLV.
Additionally, there are a limited number of investigational agents being studied and developed for the treatment of chronic HDV infection, and some may have higher incidence of drug intolerability, frequent dosing, and/or drug-drug interactions, further limiting their utility. With HDV viremia being strongly associated with progression to cirrhosis (in patients with or without alanine arninotransferase elevations), HCC, liver transplantation and liver-related mortality, there continues to be an unmet need for therapies with improved efficacy to achieve and maintain suppression of viremia (HDV RNA < LLOQ [lower limit of quantification], TND [target not detected]).

Investigational Medicinal Products information

The IMPs to be used in this trial are tobevibart, elebsiran and Hepcludex® (bulevirtide).

***Tobevibart** (VIR-3434), a monoclonal antibody (mAb) targeting the antigenic loop of HBsAg, prevents viral entry and complexes circulating HBsAg to neutralize virions.*

***Elebsiran** (VIR-2218) is a synthetic, chemically modified small interfering RNA (siRNA) targeting all hepatitis B viral transcripts for degradation, including pgRNA, and is conjugated to a ligand containing 3 N-acetyl galactosamine (GalNAc) residues to facilitate delivery to the liver.*

Tobevibart + Elebsiran
Tobevibart, a monoclonal antibody, and elebsiran, an siRNA, have complementary mechanisms of action and may be additive in effect. Additionally, as HDV viremia is reduced by elebsiran, tobevibart may be able to more easily neutralize residual virus and prevent spread to uninfected hepatocytes. Combination therapy could offer a novel strategy to treat chronic HDV infection.

***Bulevirtide** (Hepcludex®), a virus entry inhibitor that targets the sodium taurocholate co-transporting polypeptide (NTCP) receptor, received full approval on 18 July 2023 in the European Union (EU) for treatment of chronic HDV therapy. Most patients on current therapies do not achieve undetectable HDV RNA and normalization of ALT (alanine aminotransferase).*
For a full description of quality aspects of tobevibart, elebsiran and BLV and for a summary of safety and efficacy data from all clinical and nonclinical studies with tobevibart, elebsiran and BLV, please refer to the tobevibart, elebsiran IBs and BLV SmPC included with this application.

Auxiliary Medicinal Products information (AxMPs)

Nucleos(t)ide reverse transcriptase inhibitor (NRTI) is a class of antiretroviral drugs used for the suppression of HBV. Participants will be on one of the following NRTI therapies: tenofovir alafenamide (taken alone or as part of fixed-dose combination therapy), tenofovir disoproxil fumarate (taken alone or as part of fixed-dose combination therapy), or entecavir.

Study Labels

The study label documents submitted for review contain an incorrect protocol number in the document references. It has not been possible to amend this protocol number prior to submission. The sponsor confirms that the study labels will contain the correct protocol number (VIR-CHDV-V206) when they are printed and notes that, in the label proofs themselves a placeholder is included for this. The labels themselves are therefore considered to be correct. Please note that the emergency contact details are omitted from the labels with this information being present on the Participant Identification Card.

Study Design

Participants will be randomized in a 2:1 ratio to receive tobevibart+elebsiran or BLV active comparator.
Intervention groups include:

- *Arm 1: tobevibart (300 mg) + elebsiran (200 mg) SC Q4W; to be administered in the clinic*
- *Arm 2: BLV (2 mg) SC QD; to be dispensed in the clinic and administered at home*

Study design includes a 6-week screening period, which may be extended to 7 weeks depending on laboratory results availability, a minimum of 96 weeks of the study intervention period, followed by either 144 weeks of SVR follow-up or 144 weeks of continued study intervention through Week 240, and a 24-week safety follow-up period. After the study intervention period, tobevibart+elebsiran combination therapy is planned to be provided to

participants via a post-study drug access mechanism to be defined in the future. Participants who decide not to continue receiving tobevibart+elebsiran after the study intervention period or who prematurely discontinue study intervention (tobevibart+elebsiran or BLV) for any reason will enter a 24-week follow-up period after the early termination (ET) visit for safety assessments.

Study Population

Approximately 100 participants will be enrolled into the study in several countries. The trial population will comprise adult male and non-pregnant, non-lactating females aged ≥18 to 70≤ years with chronic HDV infection, both non-cirrhotic and cirrhotic up to METAVIR-F4/CPT-A, currently on NRTI therapy. Participants who fulfil the inclusion and exclusion criteria at screening are eligible for participation in this study.

Benefit/Risk Assessment

Detailed information about the known, potential, and expected benefits and risks, and reasonably expected AEs of tobevibart and elebsiran may be found in the respective IB. For detailed information regarding benefits and risks of BLV, refer to the BLV approved product prescribing information.

Reference Safety Information

Reference Safety Information, relating to the assessment of Suspected Unexpected Serious Adverse Reactions (SUSARs), is contained in Appendix 1 of the Tobevibart IB edition 4, dated 30 August 2024 and Appendix 1 of the Elebsiran IB edition 6, dated 30 August 2024 within the appended submission dossier. Reference Safety Information for Bulevirtide is located in the Summary of Product Characteristics section 4.8.

Independent Data Monitoring Committee (IDMC)
This study will be monitored by an IDMC, which will conduct periodic planned safety and efficacy reviews of study data, ad hoc safety review(s) as needed, as well as adjudicate laboratory ECT (defined in Section 8.4.6). Procedural details of the IDMC structure and function, frequency of meetings, and data planned for review is included in the IDMC charter. The TDMC charter is included in the submission.

Anticipated Annual safety report submission date
The anticipated Annual Safety Report (ASR) submission date, based on Development International Birth Date (DIBD):

Tobevibart (VIR-3434):
DTBD: 12 March 2020
Reporting period: 12 March through 11 March
Latest DSUR version and date: No. 4, dated 29 April 2024
Elebsiran (VIR-2218):
DIBD: 25 September2018
Reporting period: 25 September through 24 September
Latest DSUR version and date: No. 6, dated 13 November 2024

Patient-facing documents and eCOAs
Explanation on the use of Digital documents: The digital versions of Patient Brochure and Patient Guide will be available on participants' mobile phone (if they wish) once they scan the QR code, which will be available on the paper version of the same document they receive during the site visit. The content is the same as of the paper document.

Explanation on the versioning of the patient facing documents: The English source documents and the target language documents have identical footer with respect to version and date for easier crosscheck of usage of correct sponsor approved documents. The date of translation is captured in the translation certificate.

Explanation on the versioning of the eCOA documents: Once the translation is performed and system updated, the target language document printed from the system for certification purposes displays the date from the system as "Date printed" (inside the document). This document is then certified (translation verification check) and translation certificate issued identifying the document in its file name with a date the certification was perfonried.

Since different translation vendors with different processes are used for patient facing documents and eCOA, we apologise for not having unified method of identifying the documents. Kindly note that few eCOA and Patient facing Urdu translated documents are under review and will be shared with the final layout. Additionally, Tcert for the Urdu translated document VIR-CHDV-V206 (ECLIPSE 3) TSQM-9PakistanUrdudrafi04-Oct-2024 will be provided with the final layout.

Insurance

The premium bill for the insurance is available and attached for your records. The activation of the insurance policy will commence once the payment is made. We anticipate that site activation will take approximately four months i.e. after all approvals and the import license are received. Therefore, the payment has not been made yet, as the insurance coverage period would begin immediately upon payment, resulting in a loss of coverage time for 4-5 months while approvals are still pending.

AS soon as we receive the DRAP approval and the import license, we will proceed with the payment for the insurance as per the premium invoice.

NBC Approvals:

For NBC approval, please note that this is a parallel submission, and the approval will be shared once received during the review period.

In support of the clinical trial application please find enclosed the following supporting documentation:

Index No.	List of Documents
	Application on prescribed form along with Fee
1	***Investigator brochure***
1.1	*Investigator's Brochure for Elebsiran (VIR-221 8), Edition 6, dated 30 Aug 2024*
1.2	*Investigator's Brochure for Tobevibart (VIR-3434), Edition 4, dated 30 Aug 2024*
1.3	*Summary of product characteristics Hepcludex 17Jul 2023*
2	***Protocol***
2.1	*VIR-CHDV-V206_Clinical trial protocol, Original. Version 1.0, dated 19 Dec 2024*
2.2	*VIR-CHDV-V206— Protocol Signature Page (PSP)16Jan2025*
3	***Informed consent form***
3.1	*VIR-CHDV-V206 Main ICF V1.OPAK1.0 1 1Feb2025*
3.1	*VIR-CHDV-V206 Main ICF V1.OPAKI.0 1 1Feb2025 ur & Tcert*
3.2	*VIR-CHDV-V206 Liver Biopsy ICF V1.OPAK1.0 1 1Feb2025*
3.2	*VIR-CHDV-V206 Liver Biopsy ICF VI,OPAKI.0 1 1Feb2025_ur& Tcert*
3.3	*VIR-Cl-IDV-V206 PBMC Substudy ICF_V1.OPAK 1.0_1 1Feb2025*
3.3	*VIR-CHDV-V206 PBMC Substudy ICFV1.OPAKI.01 1Feb2025 ur& Tcert*
3.4	*VIR-CHDV-V206 Pregnant ICFV 1 .OPAK 1 .011 Feb2025*
3.4	*VIR-CHDV-V206 Pregnant ICFV 1 .OPAK 1 .011 Feb2025 ur& Tcert*
4	*List of Participating Countries (VIR-CHDV-V206 List of RAs _25 Feb 2025)*
5	*Phase of the trial*
6	*Quantity of Investigational Product to be imported or procured*
7	*Sites of the trial*
8	***C.V of investigators***
8.1	*CV - Dr. Saeed Hamid The Aga Khan University*
8.2	*CV - Dr. Zaigham Abbas -- Ziauddin University Hospital*
8.3	*CV- Dr. Ghias-un-Nabi Tayyab Central Park Teaching Hospital*
8.4	*CV — Dr. Rao Saad Au Khan — National University of Medical Sciences*
9	***Ethical committee approval with complete composition of committee i.e., Name and designations of the members - pending approvals***
9.1	*Ethics Review Committee Approval letter with members list - The Aga Khan University*
9.2	*Ethics Review Committee Approval letter with members list — Ziauddin University Hospital*
9.3	*Institutional Review Board Approval letter with members list — Central Park Teaching Hospital*
9.4	*Institutional Review Board and Ethics Committee Approval letter with members list — National University of Medical Sciences*
10	*Approval from National Bioethics Committee (PHRC)*
11	*11* ***GMP/QP*** *certificate along with* ***Free Sale Certificate*** *or Certificate of Pharmaceutical Product (For locally manufactured product GMP Cer,,* ***COA of the Product*** *and Registration Letter will be required)*
12.1	*Pre-clinical, clinical data & Safety Studies of Elebsiran*
12.2	*Pre-clinical, clinical data, safety studies of Tobevibart*
13	***Summary of the protocol or synopsis***
14.1	*Investigator Brochure Summary - IB VIR-2218 Edition 6 (ELEBSIRAN)*
14.2	*Investigator Brochure Summary - IB VIR-3434 Edition 4 (TOBEVIBART)*
15	*Adverse Event Reporting form* *• VIR-CHDV-V206_Safety Report Form with CRF completion guideline_V 1.0_Draft* *• VIR-CHDV-V206_UBC Pregnancy form with Postnatal follow up Draft vo.l*
16	*No. of Patients to be enrolled at each center*
17	*Name of monitors or clinical research associate*

18	Evidence of registration in country of origin Hepcludex (Bulevirtide)
19	Sample of label of Investigational Product • Master Label vial - VIR-22 18, version 1 .0 (PAK) dated 20DEC2024. • Master Label vial - VIR-3434 vial Pakistan Label Text 8Apr2025. • Master Label carton - Bulevirtide, version 2.0 dated 17Jan2025. • Master Label vial - Bulevirtide, version 2.0 (PAK) dated 17Jan2025.
5	Duration of trial
20	Undertaking on stamp paper
21	**Patient Facing Materials**
21.1	ECLIPSE 3 Study_About Clinical Research Studies BrochureVO 1 Global(en)26Jan2025
21.1	ECLIPSE 3_About Clinical Research Studies Brochure VOl PAK(ur) 26 Jan 2025 & Tcert
21.2	ECLIPSE 3 Study_Hepatitis D Brochure VOl Global(en)_26Jan2025
21.2	ECLIPSE 3_Hepatitis D Brochure VOl PAK(ur) 26Jan2025 & Tcert
21.3	ECLIPSE 3 Study_Online Advertisements Banners VOl Global(en)26Jan2025
21.3	ECLIPSE 3_Online Advertisements Banners VOl PAK(ur) 26Jan2025 & Tcert
21.4	ECLIPSE 3 Study Online Advertisements Social Media Clinical Trial Posts VOl Global(en) 30Jan2025
21.4	ECLIPSE 3_Online Advertisements Social Media_Clinical Trial Posts VOl PAK(ur)30Jan2025 & Tcert
21.5	ECLIPSE 3 Study Patient Brochure_VO I Global(en)_02Feb2U25
21.5	ECLIPSE 3 Study_Patient Brochure VOl PAK (ur) 02Feb2025 & Tcert
21.6	ECLIPSE 3 Study Participant ID Card_VOl Global(en)_26Jan2025
21.6	ECLIPSE 3_Participant ID Card VOl PAK(ur)_26Jan25 & Tcert
21.7	ECLIPSE 3 Study Participant Study Guide_VU I Global(en)02Feb2O25
21.7	ECLIPSE 3_Participant Study Guide VOl PAK(ur)_02 Feb 2025 & Tcert
21.8	ECLIPSE 3 Study_Thank You Card VOl Global(en)_26Jan2025
21.8	ECLIPSE 3_Thank You Card_VU I PAK(ur)_26Jan25 & Tcert
21.9	ECLIPSE 3 Study_Visit Reminder Card VU I Global(en)_26Jan2025
21.9	ECLIPSE 3_Visit Reminder Card VU I PAK(ur) 26Jan25 & Tcert
21.10	ECLIPSE 3_Digital Patient Brochure_VU I Global(en)_I 4Feb2025
21.10	ECLIPSE 3_Digital Patient Brochure_VOl PAK(ur)_14Feb25 & Tcert
21.11	ECLIPSE 3 Study_Digital Participant Study Guide VOl Global(en)_14Feb2025
21.11	ECLIPSE 3_Digital Participant Study Guide VOl PAK(ur) 14feb25 & Tcert
21.12	Extract of the SMPC Hepcludex 2mg (bulevirtide) UK(en) 16Dec24
21.12	Extract of the SMPC Hepcludex 2mg (bulevirtide) PK(ur)_16Dec24_ur-PAK & Tcert.
22	eCOA
22.1	VIR-CHDV-V206(ECLIPSE3)CLDQ-HBVRTLenUS30Jan2025
22.1	VIR-CHDV-V206(ECLIPSE3)CLDQ-HBVRTLPK(ur) 30Jan2025 & Tcert
22.2	VIR-CHDV-V206(ECLI PSE_3) EQ-SD-S LRTLenUS3UJan2025
22.2	VIR-CHDV-V206(ECLIPSE3)EQ-5D-SLRTL (Urdu) vl .0 & Tcert
22.3	VIR-CHDV-V206(ECLIP5E3)TSQM-9RTLenUS30Jan2025
22.3	VIR-CHDV-V206(EC LIPSE3)TSQM-9PakistanUrdudraft04-Oct-2024
22.4	VIR-CHDV-V206eCOA Login Screens English v3.109Dec2022 & Tcert
22.4	VIR-CHDV-V206eCOA Login Screens_Urdu_v3 .009FEB2023& Tcert
22.5	VIR-CHDV-V206eCOA Main Menu enUS 06Feb2025
22.6	VIR-CHDV-V206(ECLIPSE3)TrainingDiaryRTLenUS3UJan2025
23	**Miscellaneous**
23.1	VIR-CHDV-V206 Study Physician Referral Letter_VOl Global(en)3OJan2O25
23.2	VIR-CHDV-V206 Study Information Slides_VU I Global(en) I 2Feb2O25
23.3	VIR-CHDV-V206(ECLI PSE 3) Study Arm Correction enUS 3UJan2O25
23.4	VIR-CHDV-V206 (ECLIPSE 3) - Unscheduled Visit Activation enUS 3OJan2O25
23.5	VIR-CHDV-V206 (ECLIPSE 3) Visit Selection enUS 3OJan2O25
23.6	VIR-CHDV-V206 ECLIPSE 3eCOADevice Label enUSU I
23.7	VIR-CHDV-V206eCOAGenericGettingStartedGuideGGSGenUSU2
23.8	VIR-CHDV-V206 Delegation Letter Pakistan, vl.U, 28 Jan 2025
23.9	VIR-CHDV-V206 List of On-Going Studies 22Jan2025
23.10	Vir ECLIPSE Program I DMC Charter Final vi . I - I 9Feb2U25 signed
23.11	VIR-CHDV-V206 Rationale for collection of Ethnic Data, dated 10 Jan 2025
23.12	VIR-CHDV-V206- Justification for the Gender Selection, dated 10 Jan 2025
23.13	VIR-CHDVV2U6GCPElebsiran statement dated 2 1 Jan 2025
23.14	VIR-CHDVV206GCPTobevibart statement dated 21 Jan 2025
23.15	Items to be imported to Pakistan
23.16	VIR-CHDV-V206_ECLIPSE 3 Pharmacy Manual vi .020Feb2025_draft

23.17	Iqvia Solutions Pakistan (Pvt) Ltd. 2025 – Invoice
23.18	Pakistan MTA VIR-CHDV-V206 lead site_draft
23.19	All PIs CNIC

IP Details:

IP	Strength	Packing size	Total Quantity	Schedule
Tobevibart (VIR-3434)	300 mg/vial	Single use vial	1 vial = 1 dose	Every 4 weeks starting at Day 1 (Q4W dosing)
Elebsiran (VIR-2218)	200 mg/mL at 0.5 mL	Single use vial	2 vials = 1 dose	Every 4 weeks starting at Day 1 (Q4W dosing)
Bulevirtide (Hepcludex)	2 mg/vial	Single use vial in a kit containing 30 vials	1 vial = 1 dose 30 vials = 1 kit	Every day starting at Day 1 (QD)

Quantity of the drug(s) to be imported:
Total medicine needs to import for subjects are mentioned below:

Assumes participants randomize 2:1 ratio to Arm 1 or Arm 2
Arm 1: Tobevibart + Elebsiran for duration of study (11 participants)
Arm 2: Bulevirtide for 48 weeks and then Tobevibart + Elebsiran for remaining duration (5 participants)

IP Calculation: Treatment Plan
Arm 1: Tobevibart + Elebsiran (11 participants)
Assumes a 2-year time period for the import license.
2 years = 104 weeks
104 weeks / 4 weeks (Q4W dosing) = 26 doses

IP	No. of Patients	Per Patient Dose	Frequency	Total
Tobevibart	11	300 mg / dose	Q4W (26 doses over 2 years)	286 vials
Elebsiran	11	200 mg / dose	Q4W (26 doses over 2 years)	572 vials

Total dose for Tobevibart = 11 x 26 = 286 vials
Total dose for Elebsiran = As 2 vials is equal to 1 dose, so 26 x 2 = 52 vials, for 11 patients = 11 x 52 = 172 vials

Arm 2: Bulevirtide for 48 weeks and then Tobevibart + Elebsiran for remaining duration of study (5 participants)

Assumes a 2-year time period for the import license
2 years = 104 weeks
Participants dose on Bulevirtide for 48 weeks
48 weeks' x 7 days/week = 336 days' x 1 dose/day (QD dosing) = 336 doses
Participants dose on Tobevibart ± Elebsiran for 56 weeks (104 weeks —48 weeks = 56 weeks)
56 weeks / 4 weeks (Q4W dosing) = 14 doses

IP	No. of Patients	Per Patient Dose	Frequency	Total
Bulevirtide	5	2 mg / dose	QD (336 doses over 48 weeks)	1680 vials (56 kits)
Tobevibart	5	300 mg / dose	Q4W (14 doses over 56 weeks)	70 vials
Elebsiran	5	200 mg / dose	Q4W (14 doses over 56 weeks)	140 vials

Total dose for Bulevirtide = 5 Participants x 336 doses = 1680 vials
1680 vials / 30 vials per kit = 56 kits of Bulevirtide

Total dose for Tobevibart = 5 Participants x 14 doses = 70 vials
Total dose for Elebsiran = As 2 vials is equal to 1 dose, so 14 doses x 2 vials/dose = 28 vials. for 5 patients = 5 x 28 = 140 vials

Wastage and Damage % will be 50%:

Tobevibart: 286 vials (Arm 1) + 70 vials (Arm 2) = 356 vials
Tobevibart: 356 vials x 50% = 178 vials
Tobevibart Total Import Quantity: 356 vials + 178 vials = 534 vials

Elebsiran: 572 vials (Arm 1) -- 140 vials (Arm 2) = 712 vials
Elebsiran: 712 vials x 50% = 356 vials
Elebsiran Total Import Quantity: 712 vials + 356 vials = 1,068 vials

Bulevirtide: 1680 vials (56 kits) x 50% = 840 vials (28 kits)
Bulevirtide Total Import Quantity: *1680 vials (56 kits) + 840 vials (28 kits) = 2520* ***vials (84 kits)***

Manufacturer's name and address as per COA and GMP & packaging site and address:

IP	***Manufacturer***	***Packaging Site***
Tobevibart (VIR-3434)	*Vetter Pharma-Fertigung GmbH & Co. KG Mooswiesen 2 88214 Ravensburg, Germany*	*Fisher Clinical Services GmbH Steinbuhlweg 69 Allschwil, Switzerland*
Elebsiran (VIR-2218)	*Ajinomoto Althea Inc., (dba Ajinomoto Bio-Pharma Services), 11 040 Roselle Street, San Diego CA 92121 USA*	*Fisher Clinical Services, Inc. 699 N. Wheeling Rd., Mt. Prospect, IL, 60056*
Bulevirtide (Hepcludex)	*Gilead Sciences Ireland UC, IDA Business and Technology Park Carrigtohill Co. Cork, Ireland*	*Fisher Clinical Services GmbH Steinbuhlweg 69, Allschwil, Switzerland*

Batch & Expiry:

IP	***Manufacturing Lot***	***Current Expiry Date***
Bulevirtide (Hepcludex) Note: These are example lot numbers & expiry dates	*10005988*	*05/2026*
	10006476	*05/2026*
	10006478	*05/2026*
	10007465	*05/2026*
	10007463	*07/2026*
	10007993	*07/2026*
Tobevibart (VIR-3434)	*VYWK02*	*27-May-26*
	VYXG01	*02-Jan-27*
Elebsiran (VIR-2218)	*1-FIN-4037*	*29-Nov-26*
	1-FIN-5094	*20-Jun-27*
	1-FIN-6070	*18-Jul-28*
	1-FIN-6070A	*18-Jul-28*
	1-FIN-6103	*06-Aug-28*

Additional Information:

This is a competitive enrolment. The medicine or ready batch with the longest expiry date will be provided upon approval/import, contingent on the receipt of DRAP approval. The batch supplied will originate from the same facility as specified in the submitted documentation, maintaining the same molecule and strength. However, the batch number or lot number may be subject to change at the time of approval.

Should you have any queries regarding the enclosed application please feel free to contact the undersigned.

We look forward to hearing from you as soon as possible.

Yours sincerely,

03. The details regarding the trial, sponsor & responsible party is as follows:

i. **Sponsor:** *Vir. Biotechnology, Inc.*

ii. **Purpose of trial:** *The purpose of the study is to (1) evaluate the efficacy and safety of tobevibart+Elebsiran combination therapy compared with BLV, and (2) evaluate the efficacy of tobevibart+Elebsiran in achieving SVR following tobevibart+elebsiran interruption after 96 weeks. The primary efficacy endpoint for Part 1 is HDV RNA < LLOQ, TND at Week 48 in participants receiving tobevibart+elebsiran versus BLV. An interim analysis may be conducted when at least 60% of participants complete Week 48 assessments. The primary endpoint for Part 2 is HDV RNA <LLOQ, TND 24 weeks after the interruption of tobevibart+elebsiran. Participants will be followed for 3 years following tobevibart+elebsiran interruption to assess the durability of SVR.*

Hepatitis D virus (HDV) is a defective, hepatotropic pathogenic agent dependent on hepatitis B surface antigen (HBsAg) to complete its replication cycle and sustain infection. The global prevalence of HDV is estimated to be at least 12 million people worldwide.
Chronic HDV infection is the most aggressive form of viral hepatitis due to rapid progression to cirrhosis, liver failure, hepatocellular carcinoma (HCC), and death. Results from a recent meta-analysis examining the association between HDV RNA detectability, liver morbidity and mortality showed that persons with detectable HDV RNA were at higher risk of experiencing liver-related events, including developing cirrhosis, HCC and undergoing liver transplantation, and were at higher risk of mortality compared to those with undetectable HDV RNA.
Conversely, the loss of detectable HDV RNA is strongly associated with a lower likelihood to experience liver-related complications, and long-term suppression of HDV RNA is associated with more favourable clinical outcomes. HDV viral suppression is the most indicative surrogate marker for improved long-term clinical outcomes in patients with chronic HDV infection.
Available treatment options for HDV infection are limited to pegylated-interferon alpha (PEG-IFNα) and in some regions of the world, BLV.
Additionally, there are a limited number of investigational agents being studied and developed for the treatment of chronic HDV infection, and some may have higher incidence of drug intolerability, frequent dosing, and/or drug-drug interactions, further limiting their utility. With HDV viremia being strongly associated with progression to cirrhosis (in patients with or without alanine aminotransferase elevations), HCC, liver transplantation and liver-related mortality, there continues to be an unmet need for therapies with improved efficacy to achieve and maintain suppression of viremia (HDV RNA < LLOQ [lower limit of quantification], TND [target not detected]).

iii. **Quantity of IMPs required along with justification:**

IP	Strength	Packing size	Total Quantity	Schedule
Tobevibart (VIR-3434)	300 mg/vial	Single use vial	1 vial = 1 dose	Every 4 weeks starting at Day 1 (Q4W dosing)
Elebsiran (VIR-2218)	200 mg/mL at 0.5 mL	Single use vial	2 vials = 1 dose	Every 4 weeks starting at Day 1 (Q4W dosing)
Bulevirtide (Hepcludex)	2 mg/vial	Single use vial in a kit containing 30 vials	1 vial = 1 dose 30 vials = 1 kit	Every day starting at Day 1 (QD)

- **Quantity of the drug(s) to be imported:**

Total medicine needs to import for subjects are mentioned below:

Assumes participants randomize 2:1 ratio to Arm 1 or Arm 2
Arm 1: Tobevibart + Elebsiran for duration of study (11 participants)
Arm 2: Bulevirtide for 48 weeks and then Tobevibart + Elebsiran for remaining duration (5 participants)

- **IP Calculation: Treatment Plan**

Arm 1: Tobevibart + Elebsiran (11 participants)
Assumes a 2-year time period for the import license.
2 years = 104 weeks
104 weeks / 4 weeks (Q4W dosing) = 26 doses

IP	No. of Patients	Per Patient Dose	Frequency	Total
Tobevibart	11	300 mg / dose	Q4W (26 doses over 2 years)	286 vials
Elebsiran	11	200 mg / dose	Q4W (26 doses over 2 years)	572 vials

Total dose for Tobevibart = 11 x 26 = 286 vials
Total dose for Elebsiran = As 2 vials is equal to 1 dose, so 26 x 2 = 52 vials, for 11 patients = 11 x 52 =

172 vials

Arm 2: Bulevirtide for 48 weeks and then Tobevibart + Elebsiran for remaining duration of study (5 participants)

Assumes a 2-year time period for the import license
2 years = 104 weeks
Participants dose on Bulevirtide for 48 weeks
48 weeks' x 7 days/week = 336 days' x 1 dose/day (QD dosing) = 336 doses
Participants dose on Tobevibart ± Elebsiran for 56 weeks (104 weeks —48 weeks = 56 weeks)
56 weeks / 4 weeks (Q4W dosing) = 14 doses

IP	No. of Patients	Per Patient Dose	Frequency	Total
Bulevirtide	5	2 mg / dose	QD (336 doses over 48 weeks)	1680 vials (56 kits)
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Elebsiran	5	200 mg / dose	Q4W (14 doses over 56 weeks)	140 vials

Total dose for Bulevirtide = 5 Participants x 336 doses = 1680 vials
1680 vials / 30 vials per kit = 56 kits of Bulevirtide
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Wastage and Damage % will be 50%:

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Tobevibart: 356 vials x 50% = 178 vials
Tobevibart Total Import Quantity: 356 vials + 178 vials = 534 vials

Elebsiran: 572 vials (Arm 1) -- 140 vials (Arm 2) = 712 vials
Elebsiran: 712 vials x 50% = 356 vials
Elebsiran Total Import Quantity: 712 vials + 356 vials = 1,068 vials

Bulevirtide: 1680 vials (56 kits) x 50% = 840 vials (28 kits)
Bulevirtide Total Import Quantity: *1680 vials (56 kits) + 840 vials (28 kits) = 2520* ***vials (84 kits)***

- ***Manufacturer's name and address as per COA and GMP & packaging site and address:***

IP	Manufacturer	Packaging Site
Tobevibart (VIR-3434)	Vetter Pharma-Fertigung GmbH & Co. KG Mooswiesen 2 88214 Ravensburg, Germany	Fisher Clinical Services GmbH Steinbuhlweg 69 Allschwil, Switzerland
Elebsiran (VIR-2218)	Ajinomoto Althea Inc., (dba Ajinomoto Bio-Pharma Services), 11 040 Roselle Street, San Diego CA 92121 USA	Fisher Clinical Services, Inc. 699 N. Wheeling Rd., Mt. Prospect, IL, 60056
Bulevirtide (Hepcludex)	Gilead Sciences Ireland UC, IDA Business and Technology Park Carrigtohill Co. Cork, Ireland	Fisher Clinical Services GmbH Steinbuhlweg 69, Allschwil, Switzerland

- ***Batch & Expiry:***

IP	Manufacturing Lot	Current Expiry Date
Bulevirtide (Hepcludex) Note: These are example lot numbers & expiry dates	10005988	05/2026
	10006476	05/2026
	10006478	05/2026
	10007465	05/2026
	10007463	07/2026
	10007993	07/2026
Tobevibart (VIR-3434)	VYWK02	27-May-26
	VYXG01	02-Jan-27
Elebsiran (VIR-2218)	1-FIN-4037	29-Nov-26
	1-FIN-5094	20-Jun-27
	1-FIN-6070	18-Jul-28
	1-FIN-6070A	18-Jul-28

	1-FIN-6103	06-Aug-28

iv. ***Number of subjects to be recruited:*** *In Pakistan 16 Subjects will be enrolled (Competitive Enrollment) 04 Subjects will be enrolled at each site (04 Sites)*

v. ***Anticipated cost of the project:*** *USD 438,104/-*

vi. ***Study design & details:***

Study type	*Interventional (Clinical Trial)*
Estimated Enrollment :	*In Pakistan 16 Subjects will be enrolled (Competitive Enrollment) 04 Subjects will be enrolled at each site (04 Sites)*
Allocation:	*Randomized*
Intervention Model:	*Parallel Assignment*
Masking:	*Open Label*
Masking Description	*None*
Primary Purpose:	*Treatment*
Conditions	*Hepatitis D Virus*

vii. ***Arms and Interventions:***

Participant Group/Arm	***Intervention/Treatment***
To evaluate the long-term impact of tobevibart+elebsiran on ALT in participants with chronic HDV infection and the impact of systematic tobevibart+Elebsiran interruption per protocol on ALT	• *Change from baseline in ALT at Week 96, Week 120, Week 144, Week 192 and Week 240* • *Change from baseline in ALT from tobevibart+elebsiran interruption at Week 96 to Week 120, Week 144, Week 192 and Week 240*
To evaluate liver stiffness in participants with chronic HDV infection after long-term treatment with tobevibart+elebsiran and in participants who systematically interrupt tobevibart+elebsiran treatment per protocol	• *Change from baseline in liver stiffness as measured by liver elastography at Week 96, Week 120, Week 144, Week 192 and Week 240*
To evaluate end stage liver disease outcomes in participants with chronic HDV infection after longterm treatment with tobevibart+elebsiran and in participants who systematically interrupt tobevibart+elebsiran treatment per protocol	• *Incidence of decompensated cirrhosis (clinical event or CPT score≥ 7) by Week 96, Week 120, Week 144, Week 192 and Week 240* • *Incidence of HCC and progression to liver failure requiring transplantation or resulting in death by Week 96, Week 120, Week 144, Week 192 and Week 240*
To assess the antiviral effect of tobevibart+Elebsiran on serum HBsAg after long-term treatment with tobevibart+elebsiran and in participants who systematically interrupt tobevibart+elebsiran treatment per protocol	• *Categorical summary of HBsAg at Week 96, Week 120, Week 144, Week 192 and Week 240* • *Change from baseline in HBsAg at Week 96, Week 120, Week 144, Week 192 and Week 240*

viii. ***Overall Study Design:***

This is a Phase 2b, prospective, multicenter, randomized, open-label study evaluating the efficacy and safety of tobevibart+elebsiran compared with BLV in adult participants? 18 years with chronic HDV infection on nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy active against HBV

Participants with chronic HDV infection who are non-cirrhotic (with any level of liver fibrosis) or have compensated cirrhosis (CPT-A) will be randomized 2:1 to receive

tobevibart (300 mg) + elebsiran (200 mg) SC every 4 weeks (Q4W), or BLV (2 mg) SC daily (QD) while on background treatment with NRTI active against HBV. The randomization will be stratified by presence of cirrhosis (non-cirrhotic or compensated cirrhotic) and screening ALT (ALT <ULN or ALT> ULN).

Participants in Arm 1 who achieve HDV RNA < LLOQ, TND by Week 48 and maintain HDV RNA< LLOQ, TND between Week 48 and Week 96 will interrupt tobevibart+elebsiran starting at Week 96 (last dose of tobevibart+elebsiran at Week 92). Participants in Arm 1 who are not eligible to interrupt tobevibart+elebsiran treatment will continue to receive tobevibart+Elebsiran as chronic therapy for up to 240 weeks. All participants will continue to be monitored through laboratory and clinic evaluations as detailed in the Schedule of Activities (SoA). Participants who meet specified criteria may restart tobevibart+elebsiran.

Participants in Arm 2 (on BLV) will switch to tobevibart+elebsiran at Week 48 and continue to receive tobevibart+elebsiran through the end of study.

ix. Eligibility Criteria:

➢ ***Inclusion Criteria:*** *Participants are eligible to be included in the study only if all of the following criteria apply:*

- ***Age:***
  - *i. Adult men and women aged? 18 years (or age of legal consent, whichever is older) to 70 years at the time of signing informed consent*
- ***Type of Participant and Disease Characteristics***
  - *ii. Positive HDV antibody or positive HDV RNA PCR result for at least 6 months prior to screening and HDV RNA≥500 IU/mL at screening.*
  - *iii. Non-cirrhotic or compensated cirrhotic liver disease (up to approximately 50% of participants enrolled will be CPT-A cirrhotic) at screening.*
    - ***A.*** *Non-cirrhotic as defined by liver biopsy with METAVIR FO-F3 or liver stiffness (as measured by elastography eg, Fibroscan®) < 15 kPa within the 12 months prior to or at screening*
    - ***B.*** *Compensated cirrhotic as defined by meeting all criteria below:*
      - ***a.*** *Liver biopsy with METAVIR F4 or liver stiffness (as measured by elastography eg, Fibroscan®)? 15 and 25 kPa within the 12 months prior to screening*
      - ***b.*** *CPT score of 5 or 6, inclusive at screening*
      - ***c.*** *Compensated liver disease based on Investigator assessment*
- ***Weight:***
  - *iv. BMI? 18kg/m2 to40kg/m2*
- ***Sex and Contraceptive/Barrier Requirements***
  - *v. Female participants must have a negative pregnancy test or confirmation of postmenopausal status. CBP participants must have a negative blood pregnancy test at screening and a negative urine pregnancy test on Day 1, cannot be breast feeding, and must be willing to use highly effective methods of contraception (Section 10.6) 4 weeks before study intervention administration through 24 weeks after the last dose of study intervention. CBP participants must also agree to refrain from egg donation and in vitro fertilization from the time of study intervention administration through 24 weeks after the last dose of study intervention.*
  - *vi. Male participants with CBP partners must agree to meet 1 of the following contraception requirements from the time of study intervention administration through 24 weeks after the last dose of study intervention: vasectomy with documentation of listed for contraception for CBP participants (Section 10.6). Male participants must also agree to not donate sperm from the time of first study intervention administration through 24 weeks after the last dose of study intervention.*
- ***Informed Consent***
  - *vii. Capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol, inclusive of concomitant therapy not permitted during the study outlined in Section 6.8.1.*
- ***Other Inclusion Criteria***
  - *viii. On NRTI therapy against HBV for at least 12 weeks prior to Day 1 or have HBV DNA <20 IU/ml at screening, and currently on locally approved NRTI therapy. Participants must be on one of the following NRTI therapies: tenofovir alafenamide (taken alone or as part of fixed-dose combination therapy), tenofovir disoproxil fumarate (taken alone or as part of fixed-dose combination therapy), or entecavir.*
  - *ix. Participants with hepatic impairment with co-morbid diseases requiring medication(s) must be taking the medication(s) without a change in dose for> 3 months prior to screening. All concomitant medications must be approved by the CR0 Medical Monitor prior to study enrollment.*
  - *x. 12-lead ECG within normal limits; or, with no clinically significant abnormalities at screening, as determined by the Investigator.*
  - *xi. Agrees not to donate blood during the duration of the study and for an additional 24 weeks after the last dose of study intervention.*

➢ ***Exclusion Criteria:***

Participants are excluded from the study if any of the following criteria apply:

- ***Medical Conditions***

i. Current or prior history of any of the following:

A. Clinically significant laboratory abnormalities, co-morbid medical condition or planned medical procedure (other than HBV/HDV coinfection) that may interfere with the participant's treatment,

assessment, or compliance with the protocol. Participants under evaluation for a potentially clinically significant illness (other than HBV/HDV coinfection) are also excluded.

B. *Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy.*

C. *Current or previous (within 24 months of screening) clinically identified hepatic decompensation (eg, coagulopathy, hyperbilirubinemia, hypoalbuminemia, ascites, encephalopathy, variceal hemorrhage, hepatopulmonary or hepatorenal syndrome) or liver disease requiring paracentesis> 1 time per month or managed with Transjugular Intrahepatic Portosystemic Shunt placement.*

D. *Bone marrow, peripheral blood stem-cell or solid organ transplantation*

E. *Psychiatric hospitalization, suicide attempt, and/or a period of disability as a result of their psychiatric illness within the last 5 years. Participants with psychiatric illness that is well-controlled on a stable treatment regimen for at least 12 months prior to randomization or has not required medication in the last 12 months may be included.*

F. *Malignancy diagnosed or treated within 5 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; ductal carcinoma in situ and cervical carcinoma in situ is allowed if appropriately treated prior to screening); participants under evaluation for malignancy are not eligible.*

G. *Significant drug allergy (such as anaphylaxis or hepatotoxicity)*

ii. *One or more additional known primary or secondary causes of liver disease, other than hepatitis B or hepatitis D (i.e., alcoholism, autoimmune hepatitis, malignancy with hepatic involvement, hemochromatosis, Wilson's disease, other congenital or metabolic condition affecting the liver, congestive heart failure, etc).*

iii. *History of clinically significant immune complex disease as determined by the Investigator.*

iv. *History of anaphylaxis, allergic reactions, hypersensitivity, or intolerance to study drug, its metabolites or excipients*

v. *Participants with active HCV (participants with HCV antibodies can be enrolled if screening HCV RNA PCR test is negative).*

vi. *Participants with HIV infection (participants with HIV infection can be enrolled if CD4 T-cell counts are> 500/mm3 and HIV RNA PCR is below the limit of detection for at least 12 months).*

vii. *Participants with HAy (participants who are HAV 1gM positive can be enrolled if asymptomatic and HAV IgG positive).*

viii. *Participants with HEV (participants who are HEV 1gM positive can be enrolled if asymptomatic and HEV IgG positive). In cases where acute infection status cannot be determined by serologies a serum or stool HEV RT-PCR can be obtained. The participant is ineligible if PCR is positive.*

- ***Prior/Concomitant Therapy***

ix. *Current therapy or therapy within 24 weeks of screening with an immunomodulatory agent (eg, IFN-a), immune checkpoint inhibitors, immunosuppressants (eg, disease modifying anti-rheumatic drugs), cytotoxic or chemotherapeutic agent, or chronic systemic corticosteroids (equivalent of 10 mg prednisone QD).*

x. *Any previous treatment with BLV.*

xi. *Receipt of an investigational HDV antiviral (eg, lonafarnib, antisense oligonucleotide, IFN-lambda) within 24 weeks or 5 half-lives (if known), whichever is longer, of first study intervention administration or are active in the Follow-Up Period of another clinical study involving interventional HDV treatment.*

xii. *Participants must agree not to take part in any other investigational study at any time during their participation in this study, inclusive of the Follow-Up Period.*

xiii. *Receipt of elebsiran or any siRNA targeting HBV or HDV within 24 weeks of first study intervention administration or experienced an ALT flare (ALT? 5 x LTLN) while receiving an anti-HBV or HDV siRNA.*

xiv. *Receipt of tobevibart or any antibody targeting HBV or HDV within 24 weeks or 5 half-lives (if known), whichever is longer, of first study intervention administration.*

- ***Diagnostic Assessments***

xv. *Participants with the following laboratory parameters at screening:*

a. *ALT≥5xULN*
b. *Total bilirubin > 2.0 mg/dL*
c. *Serum albumin < 28 g/L*
d. *Platelet count < 60,000 /L*

e. *INR>l.5*
f. *CrCl < 60 mL/min as estimated using Cockcroft-Gault formula*
g. *WBC Differential, Neutrophils < 1.0 x l0/ tL*

- ***Additional Exclusions***

xvi. *History or clinical evidence of alcohol or drug abuse within 6 months before screening or a positive drug screen at screening unless it can be explained by a prescribed medication (the diagnosis and prescription must be approved by the Investigator). Cannabis use is permitted.*

5. The study will be carried out at mentioned sites comprising of following primary objective(s);

Site(s)	
Aga Khan University Hospital, Karachi.	CTS-0003
Dr. Ziauddin University Hospital, Karachi	CTS-0086
Central Park Teaching Hospital, Lahore.	CTS-0049
National University of Medical Sciences, Rawalpindi.	CTS-0103

Primary Outcome Measures:

To evaluate the safety of tobevibart+elebsiran and BLV in participants with chronic HDV infection	Incidence of TEAEs and SAEs through Week 48

Secondary Outcome Measures:

To evaluate the long-term safety of tobevibart+elebsiran in participants with chronic HDV infection	Incidence of TEAEs and SAEs through Week 96, Week 120, Week 144, Week 192 and Week 240 To assess safety after systematic tobevibart+elebsiran interruption per protocol (Arm 1)
To assess safety after systematic tobevibart+elebsiran interruption per protocol (Arm 1)	Incidence of AEs, SAEs and lab abnormalities from time of tobevibart+elebsiran interruption (Week 96) through Week 120, Week 144, Week 192 and Week 240

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Prescribed Fee	Rs. 245,000/- deposited vide challan No. 60813404502, dated 03rd April, 2025
3	Investigator Brochure (s)	**Attached** • **Elebsiran** IB No. VIR-2218, Edition 6, Dated **30th August 2024. (Page 25**-129 Corr.) • **Tobevibart,** IB No. VIR-3434, Edition 4, Dated **30th August 2024.** (Page 154-272 Corr.) • HEPCLUDEX® manufactured by Gilead Sciences Ireland (Registered Product) SmPC attached.
4	Final protocol	Attached. Protocol VIR-CHDV-V206, Version-1.0, dated 19th December 2024.
5	Informed consent and participant information sheet (Urdu to English)	Attached (English and Urdu). • PARTICIPANT INFORMATION SHEET AND CONSENT FORM AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION (Page 428-511) • OPTIONAL LIVER BIOPSY SUB-STUDY PARTICIPANT INFORMATION SHEET AND CONSENT FORM (Page 512-537) • OPTIONAL PBMC SUB-STUDY PARTICIPANT INFORMATION SHEET AND CONSENT FORM (Page 538-560) • PREGNANT PARTICIPANT OR PREGNANT PARTNER OF PARTICIPANT INFORMATION SHEET AND CONSENT FORM (Page 561-589)

6	List of participating countries	Belgium Bulgaria, France, Germany, Italy, Moldova, Mongolia, The Netherlands, Romania, Spain, Ukraine, United Kingdom and Pakistan. * CT application applied for registration at all above mentioned countries NRAs.
7	Phase of trial.	Phase – IIb
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.	Attached.
9	Site of the trial	i. Aga Khan University Hospital, Karachi. ii. Dr. Ziauddin University Hospital, Karachi iii. Central park Teaching Hospital, Lahore. (Inspection Pending) iv. National University of Medical Sciences, Rawalpindi.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB approval of following CTS are attached: i. IRB/ERC approval of **Aga Khan University Hospital, Karachi** dated 06th April, 2025 for a period of one year is attached (along with ERC Composition). ii. IRB/ERC approval of **Dr. Ziauddin University Hospital, Karachi** dated 09th April, 2025 for a period of one year is attached (along with ERC Composition). iii. IRB/ERC approval of **Central Park Teaching Hospital, Karachi** dated 07th April, 2025 for a period of one year is attached (along with ERC Composition). iv. IRB/ERC approval of **NUMS, Rawalpindi** dated 11th April, 2025 for a period of one year is attached (along with ERC Composition).
11	Approval of National Bio-ethics Committee (NBC)	Not provided and informed that NBC approval provided ASAP. Application is submitted under "Parallel Submission".
12	CV's of the Investigators	CVs of following (PI & Co-PI) experts are attached. i. Dr. Saeed Hamid (National-PI) AKUH ii. Dr. Zaigham Abbas (Site-PI) Dr. Ziauddin University iii. Dr. Ghias-Un-Nabi Tayyab (Site-PI) CPTH iv. Dr. Rao Saad Ali Khan (Site-PI) NUMS
13	GMP certificate along with COPP & free sale certificate of the investigational product.	• *BSE/TSE STATEMENT* • COA of following are attached: • Certificate of Pedigree for Hepcludex 2mg Vial • COA of following are attached: • TSE/BSE Statement for VIR-3434 • Information on Free Sale Status of Tablets • Clarification/Information on Free Sale Status of Tobevibart (VIR-3434), Elebsiran (VIR-2218) and Bulevirtide • Information on Free Sale Status of Lab Kits • GMP Compliance Certificate is attached for M/s Ajinomoto Althea, Inc., *11040 ROSELLE STREET, SANDTEGO, 92121-1205, United States.* • Declaration Concerning EMA GMP Certificate for Ajinomoto Aithea, Inc., San Diego, California, USA. • GMP Compliance Statement is attached for M/s Ajinomoto Althea, Inc. DBA Ajmomoto Bio-Pharma Services (Aji Bio-Pharma) along with FDA Establishment Identifier. • Swiss Medic CERTIFICATE OF GMP COMPLIANCE for Fisher Clinical Services GmbH, SteinbUhlweg 69, 4123 Allschwil. • Manufacturer/Importer authorization for Fisher Clinical Services GmbH, Switzerland. • QA and GMP Compliance Statement for Thermo Fisher Scientific, *Pharma Services, 7554 Schantz* Rd., *Allentown, PA USA* • *GMP Certificate is attached for M/s Fisher Clinical Services GmbH, Im Woerth 7, Weil Am Rhein, 79576, Germany.* • Manufacturer/importer Authorisation/*GMP Certificate is attached for M/s Fisher Clinical Services GmbH, Germany.* • Manufacturer's Authorisation - Investigational Medicinal Products for FISHER CLINICAL SERVICES UK LIMITED • Manufacturer/Importer Authorisation/GMP Compliance Certificate for M/s Vetter Pharma-Fertigung GmbH & Co. KG, Mooswiesen, Ravensburg, Germany. • Manufacturer/Importer Authorisation/GMP Compliance Certificate for M/s Vetter Pharma-Fertigung GmbH & Co. KG, Mooswiesen, Ravensburg, Germany. • QUALIFIED PERSON'S DECLARATION EQUIVALENCE TO EU GMP FOR INVESTIGATIONAL MEDICINAL PRODUCTS MANUFACTURED IN THIRD COUNTRIES (Details regarding manufacturer and repackers)

14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Attached
17	Adverse Event Reporting Form	Attached. • Safety Reporting Form (Version-1.0) • Serious Adverse Event Reporting Form (**VIR-CHDV-V206**) • Pregnancy Report Form (Version-1.0)
18	No. of patients to be enrolled in each center.	In Pakistan 16 Subjects will be enrolled (Competitive Enrollment) 04 Subjects will be enrolled at each site (04 Sites)
19	Name of Monitors & Clinical Research Associate	M/s IQVIA Pakistan, Karachi is appointed as CRO for the trial, following are the nominated monitor(s) for each city where proposed CTS are available: • **Karachi:** o Ayesha Jawed. o Nida Shafique • **Lahore:** o Muhammad Asif Abdullah Mir. o Hasina Sarwar. o Mahir Ahmad Khan • **Islamabad:** o Sadia Hashmi. o Asjid All Arshad. o Naila Khan. o Sidra Rashid. o Fatima Siraj
20	Evidence of registration in country of origin.	Hepdudex *(bulevirtide)* SmPC along with Market Authorization is attached.
21	Copy of registration letter (if registered in Pakistan)	Not applicable
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	6 Years 5 Months & 18 Days. (Global)
23	Undertaking on Stamp paper	Attached.

7. Applicant also attached following additional documents:

i. ECLIPSE I Study COVER LETTER (About Clinical Research Studies) (English & Urdu)
ii. ECLIPSE I Study COVER LETTER (Patient and Clinician Hepatitis D Brochure) (English & Urdu)
iii. ECLIPSE I Study COVER LETTER (Online Advertisements (Banners) for Sites) (English & Urdu)
iv. ECLIPSE I Study COVER LETTER (Online Advertisements (Social Media & Clinical Trial Posts) for Sites) (English & Urdu)
v. ECLIPSE I Study COVER LETTER (Patient Brochure_V1.0) (English & Urdu)
vi. ECLIPSE I Study COVER LETTER (Participant ID Card) (English & Urdu)
vii. ECLIPSE I Study COVER LETTER (Participant Study Guide) (English & Urdu)
viii. ECLIPSE I Study COVER LETTER (Thank You Card) (English & Urdu)
ix. ECLIPSE I Study COVER LETTER (Visit Reminder Card) (English & Urdu)
x. ECLIPSE I Study COVER LETTER (Digital Patient Brochure) (English & Urdu)
xi. ECLIPSE I Study COVER LETTER (Digital Participant Study Guide) (English & Urdu)
xii. Package leaflet: Information for the patient, Hepcludex 2 mg powder for solution for injection (English & Urdu)
xiii. The Chronic Liver Disease Questionnaire-Hepatitis B (CLDQ-HBV) (English & Urdu)
xiv. RTL Requirements English (English)
xv. Health Questioner (English & Urdu)
xvi. eCOA Login Screen Vir Biotechnology VIR-CHDV-V206 TSQM-9 RTL Requirements English US (English & Urdu)
xvii. Device Login Screens (English & Urdu)
xviii. Other online Screens (English & Urdu)
xix. PI and Site PI's CNIC.
xx. ECLIPSE I Study COVER LETTER (Physician Referral Letter_V1.0) (English)
xxi. Vir Biotechnology VIR-CHDV-V206 Study Arm Correction Requirements (English)
xxii. Vir Biotechnology VIR-CHDV-V206 Unscheduled Activation Requirements (English)
xxiii. Vir Biotechnology VIR-CHDV-V206 Visit Selection Requirements (English)

xxiv. **GETTING STARTED GUIDE** (English)
xxv. Letter of Delegation (Sponsor to Iqvia) details of delegated powers/responsibilities are as follows
xxvi. **List of On-Going Studies Investigating ELEBSIRAN (VIR-2218) and TOBEVIVART (VIR-3434)**
xxvii. INDEPENDENT DATA MONITORING COMMITTEE (IDMC) CHARTER (Final v1.1)
xxviii. CONSENT TO ELECTRONIC DELIVERY AND EXECUTION OF DOCUMENTS
xxix. RATIONALE FOR COLLECTION OF ETHNIC DATA
xxx. JUSTIFICATION FOR THE CHOSEN GENDER SELECTION
xxxi. Statement on GCP compliance
xxxii. **Details of ancillary items to be imported**
xxxiii. **Index # 23.15: Items to be imported into Pakistan**
a. Investigational Product — Tobevibart *(VIR-3434)* and Elebsiran (VIR-22 18)
b. Comparator Drug — Bulevirtide (Hepcludex)
c. Lab Kits
d. eCOA Devices - Tablets Apple iPad 10th Gen *(A2757)* - 2 pieces per site.
e. Patient Facing/Site Facing Materials - patient/site-facing materials referenced in Form II will be imported and provided by the Sponsor.
xxxiv. PHARMACY MANUAL (Version 3.0 dated 14 Jan 2025)
xxxv. Insurance (Premium Bill from efu Life Insurance)
xxxvi. Material Transfer Agreement

8. Accordingly, technical documents of the trial communicated to all CSC members for review through official email on 24th April 2025.

9. The case was placed before the CSC for consideration.

Proceedings:

The CSC was apprised the study has not yet been approved by the NBC. The expert members opined that the case requires further deliberation regarding the study design and cligibility criteria for recruitment.

Decision: The CSC decided to defer the case for submission of NBC approval and further deliberation.

10. It is submitted that applicant/PI shared NBC approval Ref: No.4-87/NBCR-1256/24-25/1891, dated 15th May 2025, on 19th May 2025.

11. The case was placed before the CSC for consideration.

Proceedings:

Dr. Saeed Hamid, National-PI & Professor of Medicine Consultant Gastroenterologist Director, Clinical Trials Unit, Aga Khan University, Stadium Road, Karachi, joined the meeting through Zoom link and explained the trial design, technical aspects of the combination therapy and its importance owing to the high prevalence of the disease in Pakistan. Regarding provision of standard level of care to the subjects the PI stated that, there is as such no commercially available standard therapy for hepatitis D. However, the participants will be provided with the standard of care for Hepatitis B (as Hepatitis D progresses in patients with Hepatitis B).

Regarding the commercialization and early access to novel therapy the PI responded that this is a study comprising of six and a half years, where the participants will be given free treatment and if willing the therapy will continue even after the trial.
The PI re-assured the commitment for early access of registered medicine in Pakistan.

Decision:

The CSC after deliberation decided to approve the Clinical Trial titled, "A Phase 2b Randomized, Open-Label Study to Evaluate the Efficacy and Safety of

Tobevibart+Elebsiran Combination Therapy Versus Bulevirtide in Participants with Chronic HDV Infection (Eclipse 3)" to be conducted at following Clinical Trial Sites:

- **Aga Khan University Hospital, Karachi. CTS-0003**
- **Dr. Ziauddin University Hospital, Karachi CTS-0086**
- **National University of Medical Sciences, Rawalpindi. CTS-0103**
- **Central Park Teaching Hospital, Lahore. CTS-0049**

2. The Committee also approved following quantity of IMPs and auxiliary items to be imported for the trial:

- ***IMPs***

IP	*No. of Patients*	*Per Patient Dose*	*Frequency*	*Total*
Bulevirtide	*5*	*2 mg / dose*	*QD (336 doses over 48 weeks)*	*1680 vials (56 kits)*
Tobevibart	*5*	*300 mg / dose*	*Q4W (14 doses over 56 weeks)*	*70 vials*
Elebsiran	*5*	*200 mg / dose*	*Q4W (14 doses over 56 weeks)*	*140 vials*

Total dose for Bulevirtide = 5 Participants x 336 doses = 1680 vials
1680 vials / 30 vials per kit = 56 kits of Bulevirtide
Total dose for Tobevibart = 5 Participants x 14 doses = 70 vials
Total dose for Elebsiran = As 2 vials is equal to 1 dose, so 14 doses x 2 vials/dose = 28 vials. for 5 patients = 5 x 28 = 140 vials

Wastage and Damage % will be 50%:

Tobevibart: 286 vials (Arm 1) + 70 vials (Arm 2) = 356 vials
Tobevibart: 356 vials x 50% = 178 vials
Tobevibart Total Import Quantity: 356 vials + 178 vials = 534 vials

Elebsiran: 572 vials (Arm 1) -- 140 vials (Arm 2) = 712 vials
Elebsiran: 712 vials x 50% = 356 vials
Elebsiran Total Import Quantity: 712 vials + 356 vials = 1,068 vials

Bulevirtide: 1680 vials (56 kits) x 50% = 840 vials (28 kits)
Bulevirtide Total Import Quantity:** 1680 vials (56 kits) + 840 vials (28 kits) = 2520 **vials (84 kits)

Manufacturer's name and address as per COA and GMP & packaging site and address:

IP	*Manufacturer*	*Packaging Site*
Tobevibart (VIR-3434)	*Vetter Pharma-Fertigung GmbH & Co. KG Mooswiesen 2 88214 Ravensburg, Germany*	*Fisher Clinical Services GmbH Steinbuhlweg 69 Allschwil, Switzerland*
Elebsiran (VIR-2218)	*Ajinomoto Althea Inc., (dba Ajinomoto Bio-Pharma Services), 11 040 Roselle Street, San Diego CA 92121 USA*	*Fisher Clinical Services, Inc. 699 N. Wheeling Rd., Mt. Prospect, IL, 60056*
Bulevirtide (Hepcludex)	*Gilead Sciences Ireland UC, IDA Business and Technology Park Carrigtohill Co. Cork, Ireland*	*Fisher Clinical Services GmbH Steinbuhlweg 69, Allschwil, Switzerland*

- **Auxiliary Items**
  - i. **Lab Kits**
  - ii. **eCOA Devices - Tablets Apple iPad 10th Gen (A2757) - 2 pieces per site (Total 08)**
  - iii. **Patient Facing/Site Facing Materials - All patient/site-facing materials referenced in Form-II will be imported and provided by the Sponsor.**

CASE No. 3.2:

APPLICATION FOR APPROVAL OF A CLINICAL TRIAL TITLED "A PHASE 3 RANDOMIZED, OPEN-LABEL STUDY TO EVALUATE THE EFFICACY AND SAFETY OF TOBEVIBART + ELEBSIRAN COMBINATION THERAPY IN PARTICIPANTS WITH CHRONIC HDV INFECTION (ECLIPSE 1) VIR-CHDV-V203", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI, (ECLIPSE-1 Trial). F. NO.03-69/2025-CT (PS)

Application was received from Dr. Saeed Hamid, National-PI & Professor of Medicine Consultant Gastroenterologist Director, Clinical Trials Unit, Aga Khan University, Stadium Road, Karachi, received on 14th April 2025. The request has been made for approval of the subject clinical trial. Application is on prescribed Form-II, along with a fee of Rs. 245,000/- deposited vide challan no. 6783710789, dated 14th March, 2025. The trial is also listed on U.S National Trial Registry with identification number ***NCT06903338*** *(https://www.clinicaltrials.gov/study/NCT06903338).*

2. *The application is reproduced as follows:*

Re: *Clinical Trial Application -Phase 3 Study*

Protocol Title: *A Phase 3 Randomized, Open-label Study to Evaluate the Efficacy and Safety of Tobevibart + Elebsiran Combination Therapy in Participants with Chronic HDV Infection (ECLIPSE 1)*
Protocol No.: *VIR-CHDV-V203*
Sponsor: *Vir Biotechnology, Inc.*
EU CT No.: *2024-515919-22-00*

For and on behalf of the sponsor, Vir. Biotechnology, Inc., we herewith submit a clinical trial application for the above-mentioned Phase 3 protocol.

This application concerns a Phase 3 study in which it is proposed to evaluate the efficacy and safety of tobevibart (VIR-3434) + elebsiran (VIR-2218) in participants with chronic hepatitis D virus (HDV) infection with elevated alanine aminotransferase (ALT) who are non-cirrhotic or have compensated cirrhosis (CPT-A), on nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy active against hepatitis B virus (HBV). The trial is prospective, multicenter. randomized, parallel- arm, open-label study and will be executed in accordance with the protocol enclosed. The total study duration for each participant is planned to be up to 270 weeks for Arm 1 and 282 weeks for Arm 2.

Background information
Hepatitis O virus (HDV) is a defective, hepatotropic pathogenic agent dependent on hepatitis B surface antigen (HBsAg) to complete its replication cycle and sustain infection. The prevalence of HDV is estimated to be at least 12 million people worldwide. Chronic HDV infection is the most aggressive form of viral hepatitis due to rapid progression to liver failure, cirrhosis, hepatocellular carcinoma (HCC), and death. Results from a recent meta-analysis examining the association between HDV RNA detectability, liver morbidity and mortality showed that persons with detectable HDV RNA were at higher risk of experiencing liver-related events, including developing cirrhosis, hepatocellular carcinoma and undergoing liver transplantation, and were at higher risk of mortality compared to those with undetectable HDV RNA. Conversely, loss of plasma HDV RNA in HDV seropositive persons Is strongly associated with a lower likelihood to experience liver related complications, and long-term suppression of HDV RNA is associated with more favourable clinical outcomes. HDV viral suppression is the most indicative surrogate marker for improved long-term clinical outcomes in patients with chronic HDV infection. The goal of chronic HDV therapy is to reduce HDV RNA to the lowest level possible while normalizing ALT.

Additionally, there are a limited number of Investigational agents being studied and developed for the treatment of chronic HDV Infection and some may have higher incidence of drug intolerability, frequent dosing, and/or drug-drug interactions, further limiting their utility. With HDV viremia being strongly associated with progression to cirrhosis (in patients with or without ALT elevations), HCC, liver transplantation and liver-related mortality. there continues to be an unmet need for therapies with Improved efficacy to achieve and maintain suppression of viremia (HDV RNA < LLOQ [lower limit of quantification), TND [target not detected)).

Investigational Medicinal Products information
The I MPs to be used in this trial are tobevibart and elebsiran.
Tobevibart (VIR-3434), a monoclonal antibody (mAb) targeting the antigenic loop of HBsAg, prevents viral entry and complexes circulating HBsAg to neutralize virions.

Elebsiran (VIR-2218) is a synthetic, chemically modified siRNA targeting all hepatitis B viral transcripts for degradation, including pg RNA, and is conjugated to a ligand containing 3 N-acetyl galactosamine (GalNAc) residues to facilitate delivery to the liver.

Tobevibart + Elebsiran

Tobevibart, a monoclonal antibody, and elebsiran, an siRNA, have complementary mechanisms of action and may be additive in effect. Additionally, as HDV viremia is reduced by elebsiran, tobevibart may be able to more easily neutralize residual virus and prevent spread to uninfected hepatocytes. Combination therapy could offer a novel strategy to treat chronic HDV infection.

For a full description of quality aspects of tobevibart and elebsiran, please refer to the IMPDs included with this application. All appropriate GMP certifications and supporting documentation have been provided with this application for your reference. For a summary of safety and efficacy data from all clinical and nonclinical studies with tobevibart and elebsiran, please refer to the IBs included with this application.

Auxiliary Medicinal Products information (AxMPs)

Nucleos(t)ide reverse transcriptase inhibitor (NRTI) is a class of antiretroviral drugs used for the suppression of HBV. Participants will be on one of the following NRTI therapies: tenofovir alafenamide (taken alone or as part of fixed-dose combination therapy), tenofovir disoproxil fumarate (taken alone or as part of fixed-dose combination therapy), or entecavir.

Study Design

Participants will be randomized 2: 1 to receive immediate treatment with tobevibart (300 mg) + elebsiran (200 mg) SC 04W for 240 weeks (Arm 1), or 12-week delayed treatment followed by tobevibart (300 mg) + elebsiran (200 mg) SC Q4W for 240 weeks (Arm 2). The randomization will be stratified by presence of cirrhosis (non-cirrhotic or compensated cirrhotic).

Intervention groups include:

- *Arm 1: tobevibart (300 mg) + elebsiran (200 mg) SC 04W starting at Day 1*
- *Arm 2: tobevibart (300 mg) + elebsiran (200 mg) SC Q4W starting at Week 12*

All participants will receive study drugs up to 240 weeks.

Study Population

This is a global study with planned participation from approximately 60 sites in several countries including EU and the US. The target sample size will be approximately 120 participants. The sample size for Pakistan is approximately 28 randomized patients (45 screened). The trial population will be comprised of male and female patients □18 and go years of age with positive HDV antibody or positive HDV RNA PCR result for at least 6 months prior to screening and HDV RNA ≥ 500 IU/ml at screening and non-cirrhotic or compensated cirrhotic liver disease at screening.

Benefit/Risk Assessment

The overall benefit-risk assessment of tobevibart + elebsiran is supported by studies in healthy participants, participants with chronic HBV infection, and participants with chronic HDV infection. The available data collected in tobevibart and elebsiran indicate clinical benefit in the target population given the demonstrated efficacy in HDV RNA suppression and ALT normalization (detailed information may be found in the tobevibart and elebsiran IBs).

Considering the measures taken to minimize risks to participants enrolled in this study, the potential risks associated with tobevibart and elebsiran are justified by the anticipated benefits that may be afforded to participants with chronic HDV infection. The benefit-risk assessment supports further evaluation of tobevibart + elebsiran in this study to fill the urgent unmet need for treatment of chronic HDV infection.

Reference Safety Information

Reference Safety Information, relating to the assessment of Suspected Unexpected Serious Adverse Reactions (SUSARs), is contained in Appendix 1 of the Tobevibart /8 edition 4, dated 30 August 2024 and Appendix 1 of the Elebsiran 18 edition 6, dated 30 August 2024 within the appended submission dossier.

Independent Data Monitoring Committee (IDMC)

The study will be monitored by an IDMC, which will conduct periodic planned safety and efficacy reviews of study data, ad hoc safety reviews as needed, as well as adjudicate Events of Clinical Interest (ECI defined in Section 8.4.6 of the Protocol). Procedural details of the IDMC structure and function, frequency of meetings, and data planned for review will be included in the IDMC charter. IDMC charter is included in the submission.

Anticipated Annual safety report submission date:

The anticipated Annual Safety Report (ASR) submission date, based on Development International Birth Date (DIBD):

Tobevibart (VIR-3434):

DIBD: 12 March 2020
Reporting period: 12 March through 11 March
Latest DSUR version and date: No. 4, dated 29 April 2024

Elebsiran (VIR-2218):
DIBD: 25 September 2018
Reporting period: 25 September through 24 September
Latest DSUR version and date: No. 6, dated 13 November 2024

Insurance
The premium bill for the insurance is available and attached for your records. The activation of the insurance policy will commence once the payment is made. We anticipate that site activation will take approximately five months after all approvals and the import license are received. Therefore, the payment has not been made yet, as the insurance coverage period would begin immediately upon payment, resulting in a loss of coverage time for 5-6 months while approvals are still pending.

As soon as we receive the DRAP approval and the import license, we will proceed with the payment for the insurance as per the premium invoice.

Patient-facing documents and eCOAs

Explanation on the use of Digital documents: *The digital versions of Patient Brochure and Patient Guide will be available on participants' mobile phone (if they wish) once they scan the QR code, which will be available on the paper version of the same document they receive during the site visit. The content is the same as of the paper document.*

Explanation on the versioning of the patient facing documents: *The English source documents and the target language documents have identical footer with respect to version and date for easier crosscheck of usage of correct sponsor approved documents. The date of translation is captured in the translation certificate.*

Explanation on the versioning of the eCOA documents: *Once the translation is performed and system updated, the target language document printed from the system for certification purposes displays the date from the system as "Date printed" (inside the document). This document is then certified (translation verification check) and translation certificate issued identifying the document in its file name with a date the certification was performed.*

Since different translation vendors with different processes are used for Patient facing documents and eCOA, we apologise for not having unified method of identifying the documents.

Additional Information
The Applicant hereby informs that the EuroQol 5-Dimension 5-Level (EQ-5D-5L), one of the patient reported outcomes (PRO), will not be assessed during the conduct of the VIR-CHDV-V203 (ECLIPSE 1) study. This study does not include an active comparator; therefore, the EQ- 5D-5L, a standardized health related quality of life (HRQoL) instrument used for describing and valuing health across different populations, will not provide meaningful assessment. There are no new risks to participants due to the omission of the EQ-5D-5L, and the protocol will be updated at next opportunity. The Chronic Liver Disease Questionnaire - Hepatitis B (CLDQ-HBV) will be collected as planned to assess the HRQoL.

In addition, we would like to clarify that all nonclinical data referred to in the Investigator's Brochures as being conducted to Good Laboratory Practice (GLP) standards was conducted in an Organisation for Economic Co-operation and Development (OECD) country and therefore is consistent with the standards of OECD GLP.

In support of the clinical trial application please find enclosed the following supporting documentation:

Index No.	***List of Documents***
	Application on prescribed form along with Fee
1	***Investigator brochure***
1.1	*Investigator's Brochure for Elebsiran (VIR-2218), Edition 6, dated 30 Aug 2024*
1.2	*Investigator's Brochure for Tobevibart (VIR-3434), Edition 4, dated 30 Aug 2024*
2	***Protocol***
2.1	*VIR-CHDV-V203 Clinical trial protocol, Original, Version 2.0, dated 07 Nov 2024*
2.2	*VIR-CHDV-V203 — Principal Investigator Protocol Signature Page (PSP)*
3	***Informed consent form***
3.1	*VIR-CHDV-V203 Optional-liver-biopsy ICF_V3.OPAKI .0_i 8Dec2024*
3.1	*VIR-CHDV-V203 Optional-liver-biopsy ICF_V3.OPAK(ur)i .0_i 8Dec2024 & Tcert*
3.2	*VI R-CHDV-V203_Preg ICFV2.OPAKI .0_I 8Dec2024*
3.2	*VIR-CHDV-V203_Preg ICF V2.OPAK(ur)i .01 8Dec2024 & Tcert*

3.3	VI R-CHDV-V203_Main ICF_V4.OPAKI .0_i 8Dec2024
3.3	VIR-CHDV-V203_Main ICF_V4.OPAK(ur)i .0_i 8Dec2024 & Tcert
4	***List of participating countries (List of RAs VIR-CHDV-V203_1 5Jan2025)***
5	Phase & Duration of trial
6	Quantity of Investigational Product to be imported or procured
7	Sites of the trial
8	***C.V of investigators***
8.1	CV - Dr. Saeed Hamid — The Aga Khan University
8.2	CV - Dr. Zaigham Abbas — Ziauddin University Hospital
8.3	CV- Dr. Ghias-un-Nabi Tayyab — Central Park Teaching Hospital
8.4	CV - Dr. Rao Saad Ali Khan — National University of Medical Sciences
9	***Ethical committee approval with complete composition of committee i.e., Name and designations of the members - pending approvals***
9.1	Ethics Review Committee Approval letter with members list - The Aga Khan University
9.1	Ethics Review Committee Approval letter with members list — Ziauddin University Hospital
9.1	Institutional Review Board Approval letter with members list — Central Park Teaching Hospital
9.1	Institutional Review Board and Ethics Committee Approval letter with members list — National University of Medical Sciences
10	Approval from National Bioethics Committee (PHRC)
11	***GMP/QP*** certificate along with ***Free Sale Certificate*** or Certificate of Pharmaceutical Product (For locally manufactured product GMP Cer., ***COA of the Product*** and Registration Letter will be required)
12.1	Pre-clinical, clinical data & Safety Studies of Elebsiran
12.2	Pre-clinical, clinical data, safety studies of Tobevibart
13	Summary of the protocol or synopsis
14.1	Investigator Brochure Summary - IB VIR-2218 Edition 6 (ELEBSIRAN)
14.2	Investigator Brochure Summary - IB VIR-3434 Edition 4 (TOBEVIBART)
15	Adverse Event Reporting form • VIR-CHDV-V203_Safety Report Form with CRF completion guideline_V1.0_Final • VIR-CHDV-V203_UBC Pregnancy form with Postnatal follow up_FINAL_eff_15JAN2025
16	No. of Patients to be enrolled at each center
17	Name of monitors or clinical research associate
18	Sample of label of Investigational Product • Master Label Vial VIR-3434 dated 20 Sep 2024 • Master Label Vial — VIR-2218 dated 29 Aug 2024
19	Undertaking on stamp paper
20	***Patient Facing Materials***
20.1	ECLIPSE 1_About Clinical Research Studies Brochure_V02_i3Dec2024_Global(en)
20.1	ECLIPSE 1_About Clinical Research Studies Brochure_V02_13Dec2024_PAK(ur) & Tcert
20.2	ECLIPSE 1_Hepatitis D Brochure_V02 Global(en)_16Dec2024
20.2	ECLIPSE 1_Hepatitis D Brochure_V02 PAK(ur)_16Dec2024 & Tcert
20.3	ECLIPSE 1_Online Advertisements_Banners_V02 Global(en)_06Dec2024
20.3	ECLIPSE 1_Online Advertisements_Banners_V02 PAK(ur)_06Dec2024 &Tcert
20.4	ECLIPSE 1_Patient Brochure_V02 Global(en)_19Dec2024
20.4	ECLIPSE 1_Patient Brochure_V02 PAK(ur)_19Dec2024 & Tcert
20.5	ECLIPSE 1_Participant ID Card_V02 Global(en)_09Dec2024
20.5	20.5 ECLIPSE 1_Participant ID Card_V02 PAK(ur)_09Dec2024 & Tcert
20.6	20.6 ECLIPSE 1_ Participant Study Guide_V02 Global(en)_20Dec2024
20.6	20.6 ECLIPSE 1_ Participant Study Guide_V02 PAK(ur)_20Dec2024 & Tcert
20.7	20.7 ECLIPSE 1_Thank You Card_V02 Global(en)_06Dec2024
20.7	20.7 ECLIPSE 1_Thank You Card_V02 PAK(ur)_06Dec2024 & Tcert
20.8	20.8 ECLIPSE 1_Visit Reminder Card_V02 Global(en)_06Dec2024
20.8	20.8 ECLIPSE 1_Visit Reminder Card_V02 PAK(ur)_06Dec2024 & Tcert
20.9	20.9 ECLIPSE 1_Online Advertisements Social Media & Clinical Trial Posts_V02 Global(en)_19Dec2024
20.9	20.9 ECLIPSE 1_Online Advertisements Social Media & Clinical Trial Posts_V02 PAK(ur)_1 9 Dec2024 & Tcert

20.10	20.10 ECLIPSE 1_Digital Participant Study Guide_V02 Global(en)_07Jan2025
20.10	20.10 ECLIPSE 1_Digital Participant Study Guide_V02 PAK(ur)_07Jan2025 & Tcert
20.11	20.11 ECLIPSE 1_Digital Patient Brochure_V02 Global(en)_03Jan2025
20.11	20.11 ECLIPSE 1_Digital Patient Brochure_V02 PAK(ur)_03Jan2025 & Tcert
21	21 **eCOA**
21.1	21.1 Diary(questionnaire): CLDQ-HBV Vir_Biotechnology_VI R-CHDV V203_(ECLI PSE_1)_CLDQ-HBV_en US_19Nov2024
21.1	21.1 Diary (questionnaire): CLDQ-HBV Vir_BiotechnologyVIR-CHDVV203_(ECLIPSE_1)_CLDQHBV_Pak(ur)_30Dec2024 & Tcert
21.2	21.2 Training diary: Vir_Biotechnology_VIR-CHDV-V203_(ECLIPSE 1)_Training Diary_enUS 1 3Dec2024
21.2	21.2 Training diary: Vir_Biotechnology_VIR-CHDV-V203_(ECLIPSE 1)_Training Diary_Pak(ur)_23Jan2025 & Tcert
21.3	21.3 Menu Screens: VIR-CHDV-V203_Main Menu_enUS_V2.0_08Dec2024
21.3	21.3 Menu Screens: VIR-CHDV-V203 Main Menu_Pak(ur)_V2.0_01 Jan2025 & Tcert
21.4	21.4 Login Screens: eCOA Login Screens_English v3.1_09Dec2022
21.4	21.4 Login Screens: eCOA Login Screens_Pak(ur)v3.1_08Feb2023 & Tcert
22	22 Miscellaneous
22.1	22.1 ECLIPSE I Study Physician Referral Letter_V02 Global(en)_17Dec2024
22.2	22.2 ECLIPSE I Pharmacy Manual v3.0_14Jan25
22.3	22.3 FKT_VIR-CHDV-V203_MAN_v2.0
22.4	22.4 Material Transfer Agreement
22.5	22.5 Insurance Premium Invoice
22.6	22.6 Items to be imported into Pakistan
22.7	22.7 VI R-CH DV-V203_Delegation Letter_Pakistan
22.8	22.8 CRF: VIR-CHDV-V203 Unique Annotated_V1.0_19Dec2024 CRF: VIR-CHDV-V203 Unique Blank_V1.0_19Dec2024
22.9	22.9 Outline of all active trials with the same IMP, VIR-CHDV-V203_List of OnGoing Studies_21 Nov2024
22.10	22.10 DSMB Charter, Vir ECLIPSE Program IDMC Charter Final_vl.1_19Feb2025
22.11	22.11 VIR-CHDV-V203 Rationale for collection of Ethic Data, dated 11 Dec2024
22.12	22.12 VIR-CHDV-V203 Justification for the Gender Selection, dated 11Dec2024
22.13	GCP Elebsiran statement dated 09 Sep 202
22.14	GCP —Tobevibart statement dated 09 Sep 2024
22.15	US Advarra Central EC Approval
22.16	MOLDOVA_EC_Initial_ApprovaL2025Feb12_en
22.17	MOLDOVA_RA_Initial Appr Letter_2025Feb 10_en
22.18	CANADA Approval Letter_20Mar2025
22.19	CNIC of all PIs

IP Details:

IP	*Strength*	*Packing size*	*Total Quantity*	*Schedule*
Tobevibart (VIR-3434)	*300 mg/vial*	*Single use vial*	*1 vial = 1 dose*	*Every 4 weeks starting at Day 1*
Elebsiran (VIR-2218)	*200 mg/mL at 0.5 mL*	*Single use vial*	*2 vials = 1 dose*	*Every 4 weeks starting at Day 1*

Quantity of the drug(s) to be imported:
Total medicine needs to import for subjects are mentioned below:

IP Calculation: Treatment Plan
Assumes a 2-year time period for the import license.
2 years = 104 weeks
104 weeks /4 weeks (Q4W dosing) = 26 doses

IP	*No. of Patients*	*Per Patient Dose*	*Frequency*	*Total*
Tobevibart	*28*	*300 mg / dose*	*Q4W (26 doses over 2 years)*	*728 vials*

Elebsiran	***28***	*200 mg / dose*	*Q4W (26 doses over 2 years)*	*1456 vials*

Total dose for Tobevibart = 28 x 26 = 728 vials
Total dose for Elebsiran = As 2 vials is equal to I dose, so 26 x 2 = 52 vials, for 28 patients = 28 x 52 = 1456 vials
Wastage and Damage % will be 50%:
Tobevibart: 728 vials x 50% = 364 vials
Tobevibart Total Import Quantity: 728 vials + 364 vials = 1092 vials
Elebsiran: 1456 vials x 50% = 728 vials
Elebsiran Total Import Quantity: 1456 vials + 728 vials = 2184 vials

Manufacturer's name and address as per COA and GMP & packaging site and address:

IP	***Manufacturer***	***Packaging Site***
Tobevibart (VIR-3434)	*Vetter Pharma-Fertigung GmbH & Co. KG Mooswiesen 2 88214 Ravensburg, Germany*	*Fisher Clinical Services GmbH Steinbuhlweg 69 Allschwil, Switzerland*
Elebsiran (VIR-2218)	*Ajinomoto Althea Inc. (dba Ajinomoto Bio-Pharma Services) 11 040 Roselle Street, San Diego CA 92121 USA*	*Fisher Clinical Services, Inc. 699 N. Wheeling Rd., Mt. Prospect, IL, 60056*

Batch & Expiry:

IP	*Manufacturing Lot*	*Current Expiry Date*
Tobevibart (VIR-3434)	*VYWK02*	*27-May-26*
	VYXG01	*02-Jan-27*
Elebsiran (VIR-2218)	*1-FIN-4037*	*29-Nov-26*
	1-FIN-5094	*20-Jun-27*
	1-FIN-6070	*18-Jul-28*
	1-FIN-6070A	*18-Jul-28*
	1-FIN-6103	*06-Aug-28*

Additional Information:

This is a competitive enrolment. The medicine or ready batch with the longest expiry date will be provided upon approval/import, contingent on the receipt of DRAP approval. The batch supplied will originate from the same facility as specified in the submitted documentation, maintaining the same molecule and strength. However, the batch number or lot number may be subject to change at the time of approval.

Should you have any queries regarding the enclosed application please feel free to contact the undersigned.

We look forward to hearing from you as soon as possible.
Yours sincerely,

3. The details regarding the trial, sponsor & responsible party is as follows:

i. **Sponsor:** *Vir Biotechnology, Inc.*

ii. **Purpose of trial:** *This is a Phase 3, prospective, multicenter, randomized, open-label study of immediate treatment with tobevibart+elebsiran compared to 12-week delayed treatment followed by tobevibart+elebsiran in adult participants? 18 years with chronic HDV infection on nucleos(t)ide reverse transcriptase inhibitor (NRTI) therapy active against hepatitis B virus (HBV). This study will enroll participants with chronic HDV infection with elevated ALT who are noncirrhotic (with any level of liver fibrosis) or have compensated cirrhosis (CPT-A). Participants will be randomized 2:1 to receive immediate treatment with tobevibart (300 mg) + elebsiran (200 mg) SC Q4W for 240 weeks (Arm 1), or 12-week delayed treatment followed by tobevibart (300 mg) + elebsiran (200 mg) sc Q4W for 240 weeks (Arm 2). The randomization will be stratified by presence of cirrhosis (noncirrhotic or compensated cirrhotic). Up to approximately 50% of participants enrolled into the study will have compensated cirrhosis (CPTA). Participants who prematurely discontinue study intervention will be followed for safety assessments for 24 weeks from the ET visit and be transitioned to the local standard of care for chronic HDV infection. The*

purpose of the study is to evaluate the efficacy and safety of immediate versus delayed treatment with tobevibart+elebsiran combination therapy. Chronic HDV infection is the most aggressive form of viral hepatitis due to rapid progression to cirrhosis, liver failure, hepatocellular carcinoma (HCC), and death. Results from a recent meta-analysis examining the association between HDV RNA detectability, liver morbidity and mortality showed that persons with detectable HDV RNA were at higher risk of experiencing liver-related events, including developing cirrhosis, HCC and undergoing liver transplantation, and were at higher risk of mortality compared to those with undetectable HDV RNA. This study will evaluate the efficacy of tobevibart+elebsiran combination therapy in participants with chronic HDV infection. The primary efficacy objective is to evaluate the ability of 48 weeks of tobevibart+elebsiran combination therapy compared to 12 weeks of delayed treatment in achieving HDV RNA < LLOQ, TND and normalizing ALT. The key secondary efficacy endpoint is HDV RNA < LLOQ, TND at Week 48 in Arm 1 versus at Week 12 in Arm 2. The primary safety objective is to evaluate the safety of tobevibart+elebsiran combination therapy. Hepatitis D remains an important medical issue in Pakistan. It has been reported that the countrywide prevalence of HDV infection in hepatitis B surface antigen (HBsAg)-positive individuals to be 16.6% in Pakistan. So there is clear urgent unmet medical need of safe and effective new HDV treatment drugs in Pakistan

The primary rationale for this study is that evidence regarding the impact of concurrent iron and calcium supplementation on hematological and iron status during pregnancy is critically needed to inform the development of a single antenatal supplement that would increase uptake of both interventions by countries and improve adherence by pregnant women. The World Health Organization (WHO) currently recommends daily iron and folic acid (IFA) supplementation with 30 mg to 60 mg of elemental iron and 400 mcg of folic acid during pregnancy (1). Compared to IFA supplementation, MMS (typically containing 13 to 15 micronutrients, depending on the formulation) improves maternal micronutrient status and increases micronutrient transfer to the fetus (2-8). The most recent meta-analysis of MMS compared to IFA supplementation revealed a significant reduction of 15% in low birth weight, 7% in small-for-gestational age (SGA), 9% in stillbirth, 19% in early preterm birth (PTB, <34 weeks' gestation), and weaker evidence of a 4% reduction in PTB (9, 10). Acknowledging this body of evidence, and that many countries are transitioning from IFA to MMS, the WHO updated its guidelines to recommend implementation of MMS supplementation in the context of rigorous research (11).

iii. Quantity of IMPs required along with justification:

IP Details:

IP	*Strength*	*Packing size*	*Total Quantity*	*Schedule*
Tobevibart (VIR-3434)	*300 mg/vial*	*Single use vial*	*1 vial = 1 dose*	*Every 4 weeks starting at Day 1*
Elebsiran (VIR-2218)	*200 mg/mL at 0.5 mL*	*Single use vial*	*2 vials = 1 dose*	*Every 4 weeks starting at Day 1*

Quantity of the drug(s) to be imported:
Total medicine needs to import for subjects are mentioned below:
IP Calculation: Treatment Plan
Assumes a 2-year time period for the import license.
2 years = 104 weeks
104 weeks /4 weeks (Q4W dosing) = 26 doses

IP	*No. of Patients*	*Per Patient Dose*	*Frequency*	*Total*
Tobevibart	***28***	*300 mg / dose*	*Q4W (26 doses over 2 years)*	*728 vials*
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Total dose for Tobevibart = 28 x 26 = 728 vials
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Elebsiran: 1456 vials x 50% = 728 vials
Elebsiran Total Import Quantity: 1456 vials + 728 vials = 2184 vials

Manufacturer's name and address as per COA and GMP & packaging site and address:

IP	*Manufacturer*	*Packaging Site*
Tobevibart (VIR-3434)	*Vetter Pharma-Fertigung GmbH & Co. KG Mooswiesen 2 88214 Ravensburg, Germany*	*Fisher Clinical Services GmbH Steinbuhlweg 69 Allschwil, Switzerland*
Elebsiran (VIR-2218)	*Ajinomoto Althea Inc. (dba Ajinomoto Bio-Pharma Services) 11 040 Roselle Street, San Diego CA 92121 USA*	*Fisher Clinical Services, Inc. 699 N. Wheeling Rd. Mt. Prospect, IL, 60056*

Batch & Expiry:

IP	*Manufacturing Lot*	*Current Expiry Date*
Tobevibart (VIR-3434)	*VYWK02*	*27-May-26*
	VYXG01	*02-Jan-27*
Elebsiran (VIR-2218)	*1-FIN-4037*	*29-Nov-26*
	1-FIN-5094	*20-Jun-27*
	1-FIN-6070	*18-Jul-28*
	1-FIN-6070A	*18-Jul-28*
	1-FIN-6103	*06-Aug-28*

iv. Number of subjects to be recruited: *Globally 120 Subjects will be enrolled 45 Subjects will be enrolled in Pakistan (Competitive Enrollment) Approximately 11 Subjects will be enrolled at each site (04 Sites).*

v. Anticipated cost of the project: *USD 2,420,380/-*

vi. Study design & details:

Study type	*Interventional (Clinical Trial)*
Estimated Enrollment :	*Globally 120 Subjects will be enrolled 45 Subjects will be enrolled in Pakistan (Competitive Enrollment) Approximately 11 Subjects will be enrolled at each site (04 Sites).*
Allocation:	*Randomized*
Intervention Model:	*Parallel Assignment*
Masking:	*None (Open label)*
Primary Purpose:	*Treatment*
Conditions	*Hepatitis D Virus Infection*
Official Title:	*A Study to Evaluate Tobevibart + Elebsiran in Chronic HDV Infection*

vii. Arms and Interventions:

Participant Group/Arm	***Intervention/Treatment***
Experimental: Arm 1 (Tobevibart + Elebsiran) Participants will receive treatment with tobevibart + elebsiran for 240 weeks.	*Drug: Tobevibart* • *Tobevibart administered by subcutaneous injection* • *Other Names:* o *VIR-3434* *Drug: Elebsiran* • *Elebsiran administered by subcutaneous injection* • *Other Names:* o *VIR-2218*
Experimental: Arm 2 (Tobevibart + Elebsiran) Participants will receive tobevibart + elebsiran after an observational period for 240 weeks.	*Drug: Tobevibart* • *Tobevibart administered by subcutaneous injection* • *Other Names:* o *VIR-3434* *Drug: Elebsiran* • *Elebsiran administered by subcutaneous injection* • *Other Names:* o *VIR-2218*

viii. Eligibility Criteria:

Inclusion Criteria:

- *Male or female ages 18 to 70 years at screening*
- *Chronic HDV infection for >/= 6 months*
- *On NRTI therapy against HBV for at least 12 weeks prior to day 1 or have HBV DNA < 20 IU/ml at screening, currently on locally approved NRTI therapy*
- *Serum ALT > ULN and < 5x ULN*
- *Non-cirrhotic or Compensated Cirrhotic Liver Disease at screening*

Exclusion Criteria:

- *Any clinically significant chronic or acute medical or psychiatric condition that makes the participant unsuitable for participation.*
- *History of significant liver disease from non-HBV or non-HDV etiology*
- *History of allergic reactions, hypersensitivity, or intolerance to study drug, its metabolites, or excipients.*
- *History of anaphylaxis*
- *History of immune complex disease*
- *History of autoimmune disorder*
- *History or evidence of alcohol or drug abuse within 6 months before screening or a positive drug screen at screening unless it can be explained by a prescribed medication*

4. The study will be carried out at mentioned sites comprising of following primary objective(s);

S. No.	Site(s)	
i.	Aga Khan University Hospital	CTS-0003
ii.	Dr. Ziauddin University Hospital, Karachi	CTS-0086
iii.	Central Park Teaching Hospital, Lahore.	CTS-0049
iv.	National University of Medical Sciences, Rawalpindi.	CTS-0103

Primary Outcome Measures:

i. HDV RNA < Lower Limit of Quantification (LLOQ), Target Not Detected (TND) and alanine aminotransferase (ALT) normalization (ALT </= Upper Limit of Normal [ULN]) at Week 48 for Arm 1 vs at Week 12 for Arm 2 [Time Frame: Up to 48 weeks]

ii. Incidence of Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) through Week 12 [Time Frame: Up to 12 weeks]

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Prescribed Fee	Rs. 245,000/- deposited vide challan no. 6783710789, dated 25th March, 2025
3	Investigator Brochure (s)	**Attached** • **Elebsiran** IB No. VIR-2218, Edition 6, Dated **30th August 2024. (Page** 509-637 Corr.) • **Tobevibart,** IB No. VIR-3434, Edition 4, Dated **30th August 2024. (Page 638**-756 Corr.)
4	Final protocol	Attached. Protocol VIR-CHDV-V203, Version-2.0, dated 07th November 2024. * Financing & Insurance details should be part of protocol as per ICH-GCP guidelines.
5	Informed consent and participant information sheet (Urdu to English)	Attached (English and Urdu). • OPTIONAL LIVER BIOPSY SUB-STIJDY PARTICIPANT INFORMATION SHEET AND CONSENT FORM • PREGNANT PARTICIPANT OR PREGNANT PARTNER OF PARTICIPANT INFORMATION SHEET AND CONSENT FORM • PARTICIPANT INFORMATION SHEET AND CONSENT FORM AND AUTHORIZATION TO USE AND DISCLOSE PROTECTED HEALTH INFORMATION
6	List of participating countries	Canada, France, Germany, Georgia, Moldova, Mongolia, New

		Zealand, Romania, Turkey, Ukraine, United Kingdom, United States and Pakistan.
7	Phase of trial.	Phase – III
8	Quantity of drug/trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Attached. IMPs along with ancillary items like kits and iPad for eCRF will be imported.
9	Site of the trial	i. Aga Khan University Hospital, Karachi. ii. Dr. Ziauddin University Hospital, Karachi (Inspection Pending) iii. Central park Teaching Hospital, Lahore. iv. National University of Medical Sciences, Rawalpindi.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB approval of following CTS are attached: i. IRB/ERC approval of **Aga Khan University Hospital, Karachi** dated 28th February, 2025 for a period of one year is attached (along with ERC Composition). ii. IRB/ERC approval of **Dr. Ziauddin University Hospital, Karachi** dated 05th March, 2025 for a period of one year is attached (along with ERC Composition). iii. IRB/ERC approval of **Central Park Teaching Hospital, Karachi** dated 25th February, 2025 for a period of one year is attached (along with ERC Composition). iv. IRB/ERC approval of **NUMS, Rawalpindi** dated 11th April, 2025 for a period of one year is attached (along with ERC Composition).
11	Approval of National Bio-ethics Committee (NBC)	NBC approval Ref: No.4-87/NBCR-1223/24/1678, dated 10th April 2025.(for a period of one year)
12	CV's of the Investigators	CVs of following (PI & Co-PI) experts are attached. i. Dr. Saeed Hamid (National-PI) AKUH, Karachi. ii. Dr. Zaigham Abbas (Site-PI) Dr. Ziauddin University, Karachi. iii. Dr. Ghias-Un-Nabi Tayyab (Site-PI) CPTH, Lahore iv. Dr. Rao Saad Ali Khan (Site-PI) NUMS, Rawalpindi.
13	GMP certificate along with COPP & free sale certificate of the investigational product.	• COA of following are attached: • Certificate of Completion • Certificate of Completion • Certificate of Completion (For softwares) • Certificate of Completion (For iPads) • GMP Compliance Statement is attached for M/s Ajinomoto Althea, Inc. DBA Ajmomoto Bio-Pharma Services (Aji Bio-Pharma) along with FDA Establishment Identifier • GMP Certificate is attached for M/s Fisher Clinical Services Pte Ltd, Singapore. (Valid till 02nd July 2027) • Manufacturer/Importer authorization Letter of M/s Vetter Pharma-Fertigung GmbH & Co. G(0RG100011586/LOC-100022677) Situated at Vetter Pharma-Fertigung GmbH & Co KG (ORG 100011586 / LOC-100020834), Mooswiesen 2, Untereschach, Ravensburg, Baden-Wuerttemberg, 88214, Germany. • GMP Compliance Statement for **Thermo Fisher Scientific, *Pharma Services, 7554 Schantz* Rd., *Allentown, PA USA*** • GMP Compliance Certificate is attached for M/s Ajinomoto Althea, Inc., ***11040 ROSELLE STREET, SANDTEGO, 92121-1205, United States.*** • ***GMP Certificate is attached for M/s Fisher Clinical Services GmbH, Im Woerth 7, Weil Am Rhein, 79576, Germany.*** • ***GMP Certificate is attached for M/s Fisher Clinical Services GmbH, Marie-Curie-Strasse 16, Herten, Rheinfelden (Baden), 79618, Germany,*** *GPS: 47.547872, 7.739966* • ***Swiss GMDP Compliance Certificate for M/s* Fisher Clinical Services GmbH, SteinbUhiweg 69, 4123 Allschwil, Switzerland. (Page 498-499)** • **GMP Compliance Certificate for M/s Vetter Pharma-Fertigung GmbH & Co. KG, Mooswiesen 2, 88214 Ravensburg** • **Germany.** • **Importer licence issued by HSA, Singapore for M/s** FISHER CLINICAL SERVICES PTE. LTD., Singapore. • QA Statements by FISHER CLINICAL SERVICES GMBH ImWorth3. 79576 Well am Rhein, Germany.

14	Pre-clinical/clinical safety studies	Attached in IB.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Attached
17	Adverse Event Reporting Form	Attached. • Safety Reporting Form (Version-1.0) • Serious Adverse Event Reporting Form (Version-1.0) • Pregnancy Report Form (Version-1.0)
18	No. of patients to be enrolled in each center.	Globally 120 Subjects will be enrolled 45 Subjects will be enrolled in Pakistan (Competitive Enrollment) Approximately 11 Subjects will be enrolled at each site (04 Sites)
19	Name of Monitors & Clinical Research Associate	M/s IQVIA Pakistan, Karachi is appointed as CRO for the trial, following are the nominated monitor(s) for each city where proposed CTS are available: • **Karachi:** o Ayesha Jawed. o Nida Shafique • **Lahore:** o Muhammad Asif Abdullah Mir. o Hasina Sarwar. o Mahir Ahmad Khan • **Islamabad:** o Sadia Hashmi. o Asjid All Arshad. o Naila Khan. o Sidra Rashid. o Fatima Siraj
20	Evidence of registration in country of origin.	Not applicable as both drugs are not registered yet.
21	Copy of registration letter (if registered in Pakistan)	Not applicable
22	Sample of label of the investigational product / drug.	Attached.
22	Duration of trial	6 Years & 23 Days. (Global)
23	Undertaking on Stamp paper	Attached.

6. Applicant also attached following additional documents:

i. Consent to Electronic Delivery and Execution of Documents (For Required hardware and software regarding eConsent through desktop computers)
ii. Information on Free Sale Status of Tablets (*Apple iPad 10th Gen (A2757),*)2 for each site.
iii. Consent to Electronic Delivery and Execution of Documents (Guidance for Required hardware and software regarding eConsent through mobiles)
iv. Ajinomoto Aithea, Inc. DBA Ajmomoto Bio-Pharma Services (Aji Bio-Pharma)
v. ECLIPSE I Study COVER LETTER (About Clinical Research Studies) (English & Urdu)
vi. ECLIPSE I Study COVER LETTER (Hepatitis D Brochure_V02) (English & Urdu)
vii. ECLIPSE I Study COVER LETTER (Online Advertisements (Banners) for Sites) (English & Urdu)
viii. ECLIPSE I Study COVER LETTER (Patient Brochure_V02) (English & Urdu)
ix. ECLIPSE I Study COVER LETTER (Participant ID Card) (English & Urdu)
x. ECLIPSE I Study COVER LETTER (Participant Study Guide) (English & Urdu)
xi. ECLIPSE I Study COVER LETTER (Thank You Card) (English & Urdu)
xii. ECLIPSE I Study COVER LETTER (Visit Reminder Card) (English & Urdu)
xiii. Social Media Posts (Unpaid social media advertisements and clinical trial posts for sites, 19 Dec 2024 [V02 Global(en)
xiv. ECLIPSE I Study COVER LETTER (Digital Participant Study Guide) (English & Urdu)
xv. ECLIPSE I Study COVER LETTER (Digital Patient Brochure) (English & Urdu)
xvi. ECLIPSE I Study (Questioner (Vir_Biotechnology_VIR-CHDV-V203_HBV_RTL) (English & Urdu)
xvii. ECLIPSE I Study (Vir_Biotechnology_VIR-CHDVV203_(ECLIPSE_1)_Training_Diary_RTL) (English & Urdu)
xviii. ECLIPSE I Study (VIR-CHDV-V203 Main Menu_(Mobile/Tablet/Windows)) (English & Urdu)
xix. ECLIPSE I Study (eCOA Login Screens_Urdu_v3.0) (English & Urdu)

xx. Subject Case Report Forms (UAT_19DEC2024_1.0 - UNIQUE)
xxi. Subject Case Report Forms (UAT_19DEC2024_1.0 - UNIQUE)
xxii. List of On-Going Studies Investigating ELEBSIRAN (VIR-2218) and TOBEVIVART (VIR-3434)
xxiii. Independent Data Monitoring Committee (IDMC) Charter (Final V1.1)
xxiv. Consent to Electronic Delivery and Execution of Documents
xxv. Rationale for Collection of Ethnic Data
xxvi. Justification for the Chosen Gender Selection
xxvii. Statement on GCP compliance
xxviii. Electronic Record and Signature Disclosure
xxix. Statement on GCP compliance
xxx. Protocol Approval with Modifications
xxxi. Approval of a Clinical Trial on a Medicinal Product for Human Use (MOLDOVA) (Page 1473-1476/Page)
xxxii. No Objection Letter (Health Canada)
xxxiii. ECLIPSE Study COVER LETTER (for internal use by IQVIA and sponsor teams as instructions)
xxxiv. Pharmacy Manual (Version 3.0 dated 14 Jan 2025)
xxxv. Central Laboratory Manual (Protocol Version 2.0 07-Nov-2024)
xxxvi. Material Transfer Agreement
xxxvii. Insurance (Premium Bill from **efu** Life Insurance)
xxxviii. Details of ancillary items to be imported
xxxix. Index no 22.6: Items to be imported into Pakistan:

a. **Investigational Product — Tobevibart (VIR-3434) and Elebsiran (VIR-22 1 8)**
b. **Lab Kits**
c. **eCOA Devices - Tablets Apple iPad 10th Gen (A2757) - 2 pieces per site**
d. **Patient Facing/Site Facing Materials - All patient/site-facing materials referenced in Form-II will be imported and provided by the Sponsor.**

xl. Letter of Delegation (Sponsor to IQVIA) details of delegated powers/responsibilities are as follows:
Delegated responsibilities include:

a. *To select clinical research site (only DRAP-approved sites)*
b. *To carry out regulatory preparation and submissions and on-going contact with Regulatory*
c. *Authority and Ethics Committee through The Aga Khan University Hospital.*
d. *To develop and maintain all monitoring activities concerning the Study as agreed with*
e. *Sponsor at clinical research sites selected in Pakistan.*
f. *To prepare and submit documents required by the Regulatory Authorities*

xli. Letter of Delegation (Sponsor to IQVIA) details of delegated powers/responsibilities are as follows:

7. Accordingly, technical documents of the trial communicated to all CSC members for review through official email on 22nd April 2025.

8. The case was placed before the CSC for consideration.

Proceedings:

The expert members deliberated that the "material & methods" haven't been clearly chalked out in the submitted protocol. In furtherance the overall study design requires more clarification regarding arms of the study and target population. Clarification regarding method for confirmation of pregnancy is also not mentioned in the protocol.

Decision: The CSC decided to defer the case for further deliberation.

9. The case was placed before the CSC for consideration.

Proceedings:

Dr. Saeed Hamid, National-PI & Professor of Medicine Consultant Gastroenterologist Director, Clinical Trials Unit, Aga Khan University, Stadium Road, Karachi, joined the meeting through Zoom link and explained the trial design, technical aspects of the combination therapy and its importance owing to the high prevalence of the disease in Pakistan. Regarding provision of standard level of care to the subjects the PI stated that, there is as such no commercially available standard therapy for hepatitis D.

However, the participants will be provided the standard of care for Hepatitis B (as Hepatitis D progresses in patients with Hepatitis B).

Regarding the commercialization and early access to novel therapy the PI responded that this is a study comprising of six and a half years, where the participants will be given free treatment and if willing the therapy will continue even after the trial.
The PI re-assured the commitment for early access of registered medicine in Pakistan.

Decision:

The CSC after deliberation decided to approve the Clinical Trial titled, "A Phase 3 Randomized, Open-label Study to Evaluate the Efficacy and Safety of Tobevibart + Elebsiran Combination Therapy in Participants with Chronic HDV Infection (ECLIPSE 1)" to be conducted at following Clinical Trial Sites:

- **Aga Khan University Hospital, Karachi. CTS-0003**
- **Dr. Ziauddin University Hospital, Karachi CTS-0086**
- **National University of Medical Sciences, Rawalpindi. CTS-0103**
- **Central Park Teaching Hospital, Lahore. CTS-0049**

2. The Committee also approved following quantity of IMPs and auxiliary items to be imported for the trial:

- **IMPs**

IP	*Strength*	*Packing size*	*Total Quantity*	*Schedule*
Tobevibart (VIR-3434)	*300 mg/vial*	*Single use vial*	*1 vial = 1 dose*	*Every 4 weeks starting at Day 1*
Elebsiran (VIR-2218)	*200 mg/mL at 0.5 mL*	*Single use vial*	*2 vials = 1 dose*	*Every 4 weeks starting at Day 1*

Quantity of the drug(s) to be imported:
Total medicine needs to import for subjects are mentioned below:
IP Calculation: Treatment Plan
Assumes a 2-year time period for the import license.
2 years = 104 weeks
104 weeks /4 weeks (Q4W dosing) = 26 doses

IP	*No. of Patients*	*Per Patient Dose*	*Frequency*	*Total*
Tobevibart	*28*	*300 mg / dose*	*Q4W (26 doses over 2 years)*	*728 vials*
Elebsiran	*28*	*200 mg / dose*	*Q4W (26 doses over 2 years)*	*1456 vials*

Total dose for Tobevibart = 28 x 26 = 728 vials
Total dose for Elebsiran = As 2 vials is equal to 1 dose, so 26 x 2 = 52 vials, for 28 patients = 28 x 52 = 1456 vials
Wastage and Damage % will be 50%:
Tobevibart: 728 vials x 50% = 364 vials
Tobevibart Total Import Quantity: 728 vials + 364 vials = 1092 vials
Elebsiran: 1456 vials x 50% = 728 vials
Elebsiran Total Import Quantity: 1456 vials + 728 vials = 2184 vials

Manufacturer's name and address as per COA and GMP & packaging site and address:

IP	*Manufacturer*	*Packaging Site*
Tobevibart (VIR-3434)	*Vetter Pharma-Fertigung GmbH & Co. KG Mooswiesen 2 88214 Ravensburg, Germany*	*Fisher Clinical Services GmbH Steinbuhlweg 69 Allschwil, Switzerland*

Elebsiran (VIR-2218)	*Ajinomoto Althea Inc. (dba Ajinomoto Bio-Pharma Services) 11 040 Roselle Street, San Diego CA 92121 USA*	*Fisher Clinical Services, Inc. 699 N. Wheeling Rd. Mt. Prospect, IL, 60056*

- **Auxiliary Items**
  - i. **Lab Kits**
  - ii. **eCOA Devices - Tablets Apple iPad 10th Gen (A2757) - 2 pieces per site (Total 08)**
  - iii. **Patient Facing/Site Facing Materials - All patient/site-facing materials will be imported and provided by the Sponsor.**

CASE No. 3.3:

APPLICATION FOR APPROVAL OF A CLINICAL TRIAL TITLED "COMPARATIVE EVALUATION OF KA6 X-RAY HANDHELD CAMERA VERSUS CONVENTIONAL X-RAY TO SUPPORT THE DIAGNOSIS OF PULMONARY TUBERCULOSIS (TB) THROUGH CHEST X-RAY", FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. NO.03-67/2025-CT (PS)

Application was received from Dr. Muhammad Irfan, National-PI & Professor, Department of Medicine, Section Head, Pulmonary & Critical Care Medicine, Aga Khan University Hospital, Karachi, received on 23rd April 2025. The application is on prescribed Form-II, along with the prescribed processing fee of Rs. 245,000, deposited vide challan No. 00538897927, dated 27th March, 2025.

2. The application is reproduced as follows:

Dear Sir,

Please find enclosed application for DRAP approval, having been approved from the AKU Ethical Committee and the NBC Approval submission, as per Form-II with the title:
"Comparative Evaluation of KA6 X-Ray Handheld Camera Versus Conventional X-ray to support the diagnosis of Pulmonary Tuberculosis (TB) through Chest X-ray".

A total of 217 patients will be enrolled in the study. This trial is only being conducted in Pakistan and AKU is the only site. The study is estimated to last approximately 12 months, given that the sample size is achieved. The investigational product, REMEX-KA6, is a handheld, portable X-ray imaging device designed for rapid and efficient chest imaging. It serves as a cost-effective and accessible alternative to conventional X-ray machines while maintaining high diagnostic accuracy. Device will be provided by sponsor of the study i.e. Martin Dow Pvt. Ltd.

The project will be conducted according to the Declaration of Helsinki (as revised in 1996) and ICH-GCP guidelines. The safety of the trial subjects will be our major concern and no patient will be enrolled without well documented freely signed consent. The confidentiality of the trial subjects will be maintained as per local and international regulations

Best Regards,

3. The details regarding the trial, sponsor & responsible party is as follows:

- i. **Sponsor:** Martin Dow Specialties Pvt. Ltd.
- ii. **Purpose of trial:** This study aims to address key gaps in the current TB diagnostic landscape, particularly the logistical, infrastructural, and cost challenges associated with traditional diagnostic methods such as sputum analysis and large, stationary X-ray machines. Existing methods face limitations in remote, under-resourced settings where access to proper infrastructure and skilled technicians may be scarce. The KA6 X-ray Handheld Camera offers a transformative solution by making high-quality diagnostic imaging more accessible, portable, and cost-effective. By minimizing the need for large equipment and specialized infrastructure, this device enables TB screening to be carried out in decentralized locations such as rural homes and community health centers. This study will explore the operational efficiency, diagnostic accuracy, and integration potential of the KA6 Camera in real-world settings, highlighting how its deployment can help bridge the gap between healthcare access and quality TB detection in underserved populations.
- iii. **Selection Criteria**

➢ **Inclusion Criteria**

- Participants aged 18-65 years, suspected of tuberculosis based on clinical evaluation, requiring further diagnostic imaging and Sputum Xpert/MTB Rif (Gene Xpert) Test.
- Capable of undergoing imaging procedures (e.g., X-ray, CT scan) without medical contraindications such as implanted devices that interfere with imaging.
- Willing to provide a sputum sample for culture, especially if suspected of TB.
- Able and willing to provide informed consent. understanding the study procedures and risks.
- Willing to follow study procedures, attend scheduled imaging sessions, and complete satisfaction surveys.
- Participants should be in a stable medical condition, without acute exacerbations of other chronic diseases (such as uncontrolled hypertension or heart failure) that may affect imaging quality or outcomes.

➢ **Exclusion Criteria**

- Patients already on anti-tuberculosis treatment, as this could interfere with diagnostic outcomes and crossover design relevance.
- Severe chronic respiratory diseases (such as advanced COPD or lung cancer) that could confound TB diagnosis or affect imaging interpretation.
- Pregnant women are excluded due to the potential risks associated with radiation exposure during imaging.
- Participants who have a known allergy to any imaging contrast agents (if contrast imaging is used).
- Acute illness, infections, or decompensated chronic conditions (like severe heart failure or uncontrolled diabetes) that might make imaging sessions difficult or affect the study's outcome.
- Inability to follow study procedures, adhere to scheduling, or complete satisfaction surveys.
- Patients with pacemakers, metal implants, or other devices incompatible with imaging technology used in the study.
- Individuals with highly contagious active infections (apart from TB suspects) that might pose a risk to study staff or other participants.

iv. **Quantity of IMPs required along with justification:** 01 KA6 mobile X-ray device will be used for this study.

v. **Number of subjects to be recruited:** 217 Subjects (Suspected TB Patients) will be recruited).

vi. **Anticipated cost of the project:** PKR 4.8 Million.

vii. **Study design & details:**

Study Type

This study employs a cross-sectional, crossover, Validation study to evaluate the diagnostic performance of the KA6 handheld X-ray camera compared to conventional X-ray in detecting pulmonary tuberculosis (TB) through chest imaging. Each participant will undergo both imaging modalities, with the sequence potentially randomized to minimize bias. The observational nature of the study focuses on collecting data related to diagnostic accuracy, image quality and ease of use for both techniques. The crossover design allows for within-subject comparisons, reducing variability and improving the precision of the comparative assessment between the two X-ray methods

Study Setting

The study will be conducted in the outpatient department (OPD) at Agha Khan University Hospital, Karachi, where patients with suspected tuberculosis (TB) frequently visit for evaluation and management. This setting provides a diverse population of patients at high risk for TB, ensuring a representative sample for the study. The hospital is equipped with both conventional chest X-ray (CXR) systems and the necessary infrastructure to support the use of the handheld camera system for imaging. Trained radiographers and a panel of experienced radiologists will be available to perform and evaluate the imaging procedures. This setting allows for a controlled environment to compare the handheld camera system and conventional CXR system in a real world clinical context.

Study Population

A total of 217 Suspected TB patients are to be enrolled in this study. Based on the 2021 World Health Organization guidelines, chest X-rays for tuberculosis diagnosis have a reported sensitivity of 85-95% and specificity of 89-96%. To accurately estimate the sensitivity of a portable X-ray machine with a confidence level of 95%o, we used OpenEpi to calculate the required sample size. Assuming a sensitivity of 83% (within the lower range of the WHO guidelines) and a desired precision of ±5%, OpenEpi determined that a minimum of 217 subjects is required to achieve a95%o confidence interval.

This sample size ensures that the study will have sufficient power to detect the diagnostic accuracy of the portable X-ray machine with a high level of confidence.

Study Procedures

Participants who visit the outpatient department (OPD) with suspected TB will be approached for consent. Upon obtaining informed consent, participants will be screened to determine their eligibility. Those who fulfill the inclusion criteria and do not meet any of the exclusion criteria will be enrolled in the study.
Participants enrolled will undergo chest X-ray imaging using both a KA6 X-Ray handheld camera system and a conventional CXR system. The KA6 X-Ray handheld camera system, specifically designed for portable CXR imaging, and the standard CXR equipment in a radiology department will both be operated by trained radiographers.

The imaging sessions for each participant will be conducted within a short time frame, typically on the same day, to minimize changes in clinical status. The order of imaging modalities will be randomized, and each participant will serve as their own control. Radiographers will be blinded to the study hypothesis. A radiologist, also blinded to the imaging modality. will independently evaluate the in-rages using established radiological criteria to assess the presence of TB and the quality of the images on a standardized scale.

To ensure the validity of the results and the findings of the chest X-rays, the screened patients will also have to undergo the Sputum XperliMTB Rif (GeneXpert) Test for testing the same day.
Additionally, participants will complete satisfaction surveys after each imaging session to compare their comfort and experience with both systems, the illiterate participant will be assisted by study coordinator in the presence of an impartial witness in completing the survey. Radiographers will also complete satisfaction surveys to assess the ease of use and operational efficiency of each system. All collected data, including imaging, Sputum Test results, and satisfaction survey results, will be used to evaluate the diagnostic accuracy, image quality, inter-rater reliability, and user satisfaction of the handheld camera system compared to the conventional CXR system.

4. The study will be carried out at mentioned sites comprising of following primary objective(s);

Site(s)
Aga Khan University Hospital, Karachi CTS-0003

Primary Objective
To gauge the sensitivity and specificity of the KA6 X-Ray handheld camera system compared to the conventional chest X-ray (CXR) system to support the diagnosis of pulmonary tuberculosis.

Secondary Objectives
- To evaluate and compare the quality of images produced by the handheld camera system and the conventional CXR system.
- To collect feedback from participants regarding their experience and comfort with the handheld camera system compared to the conventional CXR system.
- To gather feedback from radiographers on the ease of use of the handheld camera system versus the conventional CXR system.

Endpoints
Primary Endpoint
- Sensitivity: The proportion of true positive cases correctly identified by the KA6 handheld camera system confirmed through cross reference, Sputum Xpert/MTB Rif (GeneXpert) Test.
- Specificity: The proportion of true negative cases correctly identified by the KA6 handheld camera system confirmed through cross reference, Sputum Xpert/MTB Rif (GeneXpert) Test

Secondary Endpoint
- Quality of images produced by the KA6 handheld X-Ray camera system and the conventional CXR system. as assessed by radiologists using a standardized scale
- Participant satisfaction survey comparing comfort and experience with the KA6 handheld X-Ray camera system versus the conventional CXR system.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Prescribed Fee	Not provided.
3	Investigator Brochure (s)	IB No. RETVEX-KA6, Version-1, dated 02nd March, 2021.
4	Final protocol	Attached. Protocol-KA6 X-Ray Handheld Camera vs.

		Conventional X-ray for TB Detection, Version 1.2, dated 15th Jan 2025. & CRF Version 1.0, dated 22nd October 2024.
5	Informed consent and participant information sheet (Urdu to English)	ICF Version 1.2 dated 15th January 2025 is attached (English & Urdu)
6	List of participating countries	**Pakistan only**
7	Phase of trial.	Phase-IV Post Market Surveillance This study is a Phase 4 post-marketing study. The study is designed as a cross-sectional, crossover Validation study to evaluate the diagnostic performance of the KA6 handheld X-ray camera compared to conventional X-ray in detecting pulmonary tuberculosis (TB) through chest imaging. Each participant will undergo both imaging modalities, with the sequence potentially randomized to minimize bias. The observational nature of the study focuses on collecting data related to diagnostic accuracy, image quality and ease of use for both techniques. The crossover design allows for within-subject comparisons, reducing variability and improving the precision of the comparative assessment between the two X-ray methods. The study is anticipated to last for up to 3-4 Months.
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.	Attached. 01 KA6 mobile X-ray device will be used for this study.
9	Site of the trial	CTU Aga Khan University Hospital, Karachi (CTS-0003)
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB approval of following CTS are attached: i. IRB/ERC approval of **Aga Khan University Hospital, Karachi** dated 17th January, 2025 for a period of one year is attached (along with ERC Composition).
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter No.4-87/NBCR-1212/24-25/1418, dated 10th March, 2025 for a period of **One Year** is attached.
12	CV's of the Investigators	The CVs of following (PI & Co-PI) experts are attached. i. Dr. Muhammad Irfan (PI) AKUH ii. Dr. Vaqar Bari (Co-PI) AKUH iii. Dr. Vaqar Bari PMDC Registration Letter & CITI-1RCR Course iv. Dr. Vaqar Bari PMDC Registration Letter & NIDA-GCP Certificate
13	GMP certificate along with COPP & free sale certificate of the investigational product.	The following documents are attached: i. Certificate of Manufacturer ii. CE Certificate iii. FDA Registration Certificate
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	•
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	217 Subjects (Suspected TB Patients) will be recruited.
19	Name of Monitors & Clinical Research Associate	M/s Metrics Research (Pvt.) Ltd., Karachi is appointed as CRO for the trial. The following are the nominated monitors: • Usama Sulaiman (CRA at National Hospital & Medical Center, Lahore) • Jahanzeb Muhammad Khan (CRA at Creek General Hospital, Karachi) Details of the Site PI and their approval are not attached.
20	Evidence of registration in country of origin.	The following documents are attached: i. Certificate of Manufacturer

		ii. CE Certificate iii. FDA Registration Certificate
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	03-04 Months
23	Undertaking on Stamp paper	Attached.

6. Technical documents shared with all CSC members for review through official email on 27th April 2025.

7. After initial evaluation of the case it transpired that this is a Phase-IV clinical trial of a medical device (not registered in Pakistan). Some of the observations after initial review are as under: -

i. The device operates on the principles of X-rays and radiation emission therefore regulations by PNRA (Pakistan Nuclear Regulatory Authority) need to complied.
ii. The exclusion criteria mentions "*Participants who have a known allergy to any imaging contrast agents (if contrast imaging is used)*" AND "*Patients with pacemakers, metal implants, or other devices incompatible with imaging technology used in the study*". These need some clarification.
iii. The "*User Manual*" mandates a "*trained physician*" to operate the hand held device but it's not clearly mentioned in the protocol. As a matter of practice, x-ray technicians are normally involved in image acquisition in the hospitals.
iv. The details regarding training plan for operating the hand held device are also not provided.
v. Every patient enrolled in the study will have to be exposed to the radiation twice, the impact of radiation hazard and steps taken for safety of subject needs to be further explained.
vi. Will the subject (after getting enrolled in the study) bear the cost of radiological investigation(s) or further treatment or otherwise.

8. The case was placed before the CSC for consideration.

Decision: The CSC after consideration deferred the case for the submission of following information/documents:

i. The device operates on the principles of X-rays and radiation emission therefore regulations by PNRA (Pakistan Nuclear Regulatory Authority) need to complied.
ii. The exclusion criteria mentions "Participants who have a known allergy to any imaging contrast agents (if contrast imaging is used)" AND "Patients with pacemakers, metal implants, or other devices incompatible with imaging technology used in the study". These need some clarification.
iii. The "User Manual" mandates a "trained physician" to operate the hand held device but it's not clearly mentioned in the protocol. As a matter of practice, x-ray technicians are normally involved in image acquisition in the hospitals.
iv. The details regarding training plan for operating the hand held device are also not provided.
v. Every patient enrolled in the study will have to be exposed to the radiation twice, the impact of radiation hazard and steps taken for safety of subject needs to be further explained.
vi. Will the subject (after getting enrolled in the study) bear the cost of radiological investigation(s) or further treatment or otherwise.
vii. Pregnancy testing policy for female subjects.

2. The CSC further decided and delegate its powers to the Chairman CSC to decide the case accordingly after submission of above mention information.

9. Accordingly, the CSC decision was communicated to applicant vide letter bearing No. 16-56/2025-CSC, dated 06th May 2025. In reference to the CSC decision, Dr. Muhammad Irfan, National-PI & Professor, Department of Medicine, Section Head, Pulmonary & Critical Care Medicine, Aga Khan University Hospital, Karachi submitted reply received on 14th May 2025.

10. Applicant reply is reproduced as under:

Subject: Response to DRAP letter on 06 May 2025 F.No.16-56/2025-CSC – Application for Clinical Trial Approval Titled "Comparative Evaluation of Ka6 X-Ray Handheld Camera Versus Conventional X-Ray to Support the Diagnosis of Pulmonary Tuberculosis (Tb) Through Chest X-Ray", From Aga Khan University Hospital, Karachi. F. NO.03 69/2025-CT (PS)

Please find below our response to the issues raised during the 56th CSC meeting held on April 29, 2025:

i. ***The device operates on the principles of X-rays and radiation emission therefore regulations by PNRA (Pakistan Nuclear Regulatory Authority) need to complied.***

Response: *The device is CE- and FDA-registered and is already in global clinical use. The study will be conducted at the Radiology Department of Aga Khan University Hospital (AKUH), which is a PNRA-licensed diagnostic facility under license number M401(075) (attached). This ensures that the site is already operating in accordance with PNRA's standards for radiation protection, equipment safety, and staff training. Furthermore, the device will be used strictly in compliance with PNRA's "Regulatory Guide on Radiation Safety and Regulatory Requirements in Medical Diagnostic X-ray Facilities" (PNRA-RG-904.08).*

ii. ***The exclusion criteria mentions "Participants who have a known allergy to any imaging contrast agents (if contrast imaging is used)" AND "Patients with pacemakers, metal implants, or other devices incompatible with imaging technology used in the study". These need some clarification.***
Response: *We confirm that this study does not involve the use of contrast imaging. The exclusion criterion referencing allergy to contrast agents was conservatively included as a precautionary standard in the protocol template. Additionally, patients with pacemakers, metal implants, or other devices will be excluded not due to a contraindication with the KA6 device, but to prevent any potential image quality compromise. The KA6 device poses no known interference risk with such devices.*

iii. ***The "User Manual" mandates a "trained physician" to operate the hand held device but it's not clearly mentioned in the protocol. As a matter of practice, x-ray technicians are normally involved in image acquisition in the hospitals.***

Response: *The REMEX-KA6 User Manual specifies operation by a "qualified and trained clinician with appropriate licensing" (Section 2.1), emphasizing adherence to radiation safety protocols due to the device's technical and regulatory complexities. While the term "trained physician" is not explicitly detailed in the manual, AKU—being registered with the Pakistan Nuclear Regulatory Authority (PNRA)—follows strict PNRA guidelines and institutional SOPs that align with global standards. Under PNRA's framework, certified radiologic technologists (X-ray technicians) are recognized as qualified personnel to operate diagnostic X-ray equipment, provided they undergo rigorous training in radiation safety, device-specific protocols, and exposure optimization. AKU's existing protocols ensure technicians handling the REMEX-KA6 complete manufacturer-recommended training (Section 4.2). This approach bridges the manual's general terminology with AKU's operational reality, ensuring safe use while leveraging technicians' expertise in image acquisition under radiologist oversight. By aligning with PNRA's regulations, AKU guarantees compliance with both national safety standards and the device's technical mandates, mitigating risks of overexposure or procedural errors.*

iv. ***The details regarding training plan for operating the handheld device are also not provided.***

Response: *A comprehensive training plan will be implemented prior to study initiation. All Study staff will undergo formal, hands-on training conducted by the Sponsors technical experts. This will cover device operation, radiation safety, quality assurance, and image handling. GCP Certification will be required for all users prior to participation, and training records will be maintained and made available for review.*

v. ***Every patient enrolled in the study will have to be exposed to the radiation twice, the impact of radiation hazard and steps taken for safety of subject needs to be further explained.***

Response: *The study involves participants receiving two radiation exposures: one from a conventional X-ray and another from the REMEX-KA6 portable X-ray device. The cumulative radiation dose is carefully managed to ensure safety, adhering strictly to Pakistan Nuclear Regulatory Authority (PNRA) guidelines and international standards. A conventional X-ray typically delivers an effective dose of approximately 0.01–0.1 mSv, depending on the body part and technique, while the REMEX-*

KA6's maximum dose per exposure is 46.12 μGy·m² (equivalent to ~0.05–0.1 mSv). Combined, the total dose (~0.06–0.2 mSv) remains well below PNRA's annual public dose limit of 1 mSv, posing negligible risk of deterministic or stochastic effects.

vi. ***Will the subject (after getting enrolled in the study) bear the cost of radiological investigation(s) or further treatment or otherwise.***

Response: *Study participant will not bear any cost related to imaging or study-specific procedures. All expenses will be covered by the study budget. For further treatment, the participant will be referred as per standard of care.*

vii. ***Pregnancy testing policy for female subjects.***
Response: *As part of the screening and eligibility assessment, all female participants of childbearing potential will be asked about their pregnancy status during evaluation against the exclusion criteria. If a participant reports being pregnant or is uncertain about her pregnancy status, she will be excluded from the study to avoid any potential radiation-related risks.*

11. Applicant attached License No.: M401(075), issued by PNRA, valid till 31st August 2025.

12. The case was placed before the CSC for consideration.

Decision:

The CSC after deliberation decided to approve the Clinical Trial titled, "Comparative Evaluation of KA6 X-Ray Handheld Camera Versus Conventional X-Ray to Support the Diagnosis of Pulmonary Tuberculosis (TB) Through Chest X-Ray" to be conducted at M/s Aga Khan University Hospital, Karachi (CTS-0003).

2. The Committee also approved following quantity of IMPs to be imported for the trial:

- **01 KA6 mobile X-ray device**

CASE No. 3.4:

APPLICATION FOR APPROVAL OF A PHASE-I -II CLINICAL TRIAL TITLED "A MULTICENTER, DOUBLE BLIND RANDOMIZED PLACEBO-CONTROLLED 2-ARM MIXED PHASE 1 / 2 CLINICAL TRIAL TO EVALUATE THE EFFECTS OF 2 DEOXY RIBOSE ON HEALING OF CHRONIC DIABETIC FOOT ULCERS", FROM THE CENTER FOR BIOEQUIVALENCE STUDIES AND CLINICAL RESEARCII (CBSCR) INTERNATIONAL CENTER FOR CHEMICAL AND BIOLOGICAL SCIENCES (ICCBS) UNIVERSITY OF KARACHII, KARACHII - 75270 PAKISTAN.F. No.03-60/2024-CT (PS)

Application was received from Dr. Muhammad Raza Shah PI & General Manager Center for Bioequivalence Studies and Clinical Research (CBSCR) International Center for Chemical and Biological Sciences (ICCBS) University of Karachi, Karachi, dated 9th October, 2024, wherein request has been made for approval of subject Clinical Trial. Application is on prescribed Form-II, along with a fee of Rs. 245,000/- deposited vide challan No. 09161963641, dated 8th October, 2024. The trial is not enlisted on U.S. National Trial Registry.

2. Applicant informed that, it is a multi-center trial & will be conducted in Pakistan only. The sample size for Phase –I, is 37 subjects whereas 50 subjects for phase-II. The proposed study centers are as under: -

i. Department of Plastic & Reconstructive Surgery/Mayo Burn Centre.
ii. Burn Centre, Pakistan Institute of Medical Sciences, Islamabad.

3. The details regarding the trial sponsor & responsible party is as follows:

i. **Sponsor:** Interdisciplinary Research Centre in Biomedical Materials (IRCBM) COMSATS University Islamabad Lahore Campus, 54000, Lahore, Pakistan under HEC-British council sponsored project.

ii. **Responsible Party**: Jerry Zimmerman, Seattle Children's Hospital, Washington, USA.

iii. **Purpose of trial:** to evaluate the effects of 2-deoxy-D-ribose on healing of chronic diabetic foot ulcers.

Primary Objective: To assess safety, tolerability and compare the effects of 2dDR-tulle gras dressing to tulle gras placebo-control dressing.

Secondary Objective: To compare incidence of complete healing, incidence of 40%o wound healing, the cost-effectiveness of each treatment arm, the effects of 2dDR dressing to standard of care dressing on wound-related quality of life, dressing properties in terms of ease of application, complications (allergic response, bleeding, quantity of granulation, malodor, leak, unexpected re- dressing, etc.) and patient compliance.

iv. **Arms & Interventions:**

Participant Group/Arm	Intervention/Treatment
Placebo-controlled Group	Un medicated tulle gras with a secondary dressing of a layer of fluffy cotton gauze (approximately 2cm thick) covered in a layer of cling-film. **Mode of administration**: The dressing will be applied on foot ulcer twice a week.
Normal dose intervention Group	Normal dose 2dDR-medicated tulle gras with a secondary dressing of a layer of fluffy cotton gauze (approximately 2cm thick; l0xl0 cm21 covered in a layer of cling-film. Dose: 46.25 mg (per 10x10 cm2 dressing) **Mode of administration:** The dressing will be applied on foot ulcer twice a week.
Super-normal dose intervention Group	Super-normal dose 2dDR-medicated tulle gras with a secondary dressing of a layer of fluffy cotton gauze (approximately 2cm thick) covered in a layer of cling-film. Dose: 138.75 mg (per l0xl0 cm2 dressing) **Mode of administration:** The dressing will be applied on foot ulcer twice a week.

v. **Quantity of IMPs required along with justification:**

IMPs Phase-I	Molecule	Strength	Pack Size	Manufacturer	TOTAL
2dD-tulle gras dressing (normal dose)	2-Deoxy D-ribose	Not described	Not described	Cotton Craft	404 sheets
2dDR-tulle gras dressing (super normal dose)	2 Deoxy Ribose	Not described	Not described	Cotton Craft	126 sheets
Placebo	Normal Saline	Identical in appearance, volume and smell as Active Study agent			404 sheets

IMPs Phase-II	Molecule	Strength	Pack Size	Manufacturer	TOTAL
2dDR-tulle gras dressing (normal dose)	2 Deoxy Ribose	Not described	Not described	Cotton Craft	630 sheets
Placebo	Normal Saline	Identical in appearance, volume and smell as Active Study agent			630 sheets

vi. **Number of subjects to be recruited:**

- Phase I: 37 subjects will be enrolled.
- Phase II: 50 subjects will be enrolled.

vii. **Anticipated cost of the project: 1,000,000/- PKR**

viii. **Study design & details:**

Study type	Interventional (Clinical Trial)
Estimated Enrollment :	• Phase I: 37 subjects will be enrolled. • Phase II: 50 subjects will be enrolled.
Allocation:	Randomized
Intervention Model Description:	This is a multi-center, double-blind, randomized, placebo-controlled, 2-arm, mixed phase 1/2 clinical trial to evaluate the effects of2-deoxy-d-ribose on healing of chronic diabetic foot ulcers. In phase l, patients will be randomized into three groups i.e. placebo-controlled/ un-medicated tulle gras dressing group, normal dose 2dDR-medicated tulle gras group, and supernormal dose 2dDR- medicated tulle gr-as-group in a ratio of 4:4:1. In phase 2, patients will be randomized into two

	groups i.e. placebo-controlled/un-medicated tulle gras dressing group and normal dose 2dDR-medicated tulle gras group in a ratio of 1:1. A meeting of DSMB will be held to evaluate the safety of the Phase-I clinical trial after 4 weeks of treatment-of the last subject (i.e.37 subject) enrolled in the trial. Thereafter, the DSMB will submit their recommendations for the initiation of recruitment of Phase II clinical trial to PI. After receiving recommendation from the DSMB, the PI will initiate the recruitment of the subjects in Phase II clinical trial.
Masking:	Double Blinded
Primary Purpose:	Treatment.
Official Title:	A Multicenter, Double Blind Randomized Placebo-Controlled 2-Arm Mixed Phase 1 / 2 Clinical Trial To Evaluate The Effects Of 2 Deoxy Ribose On Healing Of Chronic Diabetic Foot Ulcers

4. The study will be carried out at mentioned sites comprising of following primary objective(s);

Site(s)
CBSCR-ICCBS, Karachi (CTS-0046)

Primary Outcome Measures:

To assess safety, tolerability and compare the effects of 2dDR-tulle gras dressing to tulle gras placebo-control dressing.

Secondary Outcome Measures:

To compare incidence of complete healing, incidence of 40%o wound healing, the cost-effectiveness of each treatment arm, the effects of 2dDR dressing to standard of care dressing on wound-related quality of life, dressing properties in terms of ease of application, complications (allergic response, bleed, quality of granulation, malodor, leak, unexpected re- dressing, etc.) and patient compliance

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs. 245,000/- deposited vide challan No. 09161963641, dated 8th October, 2024.
3	Investigator Brochure (s)	Attached. IB Version No: 1.0, dated: 17 March 2023.
	Final protocol	Attached. BC-HEC/-2dDR-phase1/2 (2023)/ Protocol/1.0. Dated 04-04-2023 Unsigned Protocol is attached.
5	Informed consent and participant information sheet (Urdu to English)	ICF Version 2.0, Dated 02nd April, 2023 is Attached.
6	List of participating countries	Pakistan only.
7	Phase of trial.	Phase-I & Phase-II
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	Attached. **
9	Site of the trial	v. The Center for Bioequivalence studies and Clinical Research (CBSCR) International Center for Chemical and Biological Sciences (ICCBS) (CT-0046)
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB approval of following sites are attached: ii. IRB/ERC approval of **CBSCR-ICCBS, Karachi** dated 28th March, 2024 is attached. (Page 218-219/Corr.) iii. IRB/ERC approval of **King Edward Medical University, Lahore** dated 13th November, 2023 is attached. (Page 220/Corr.) iv. IRB/ERC approval of **Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad** dated 01st September,

		2023 is attached. (Page 221/Corr.) * Composition of IRBs of following are not attached. • King Edward Medical University, Lahore • Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter No.4-87/NBC-1110/23/376, dated 24th September 2024 for a period of **One Year** is attached for Protocol Version 1.0
12	CV's of the Investigators	CVs of following (PI & Co-PI) are attached. i. Prof. Dr. Raza Shah (National-PI) ii. Prof. Dr. Tariq Iqbal (Co-PI) (Plastic Burns & Reconstructive Surgeon, Dean Surgery &Allied SZABMU PIMS) iii. Dr. Muhammad Mustehsan Bashir, Head Burn Center KEMU/Professor of Plastic Surgery. (Co-PI) iv. Dr. Muhammad Nasir, Critical Care Physician Consultant and In-charge of ECU and ICU at Center for Bioequivalence Studies and Clinical Research-ICCBS, Karachi. (Co-PI) v. Dr. Muhammad Yar (T.I.), Tenured Associate Professor, Interdisciplinary Research Centre in Biomedical Materials (IRCBM), COMSATS University Islamabad, Lahore Campus, Pakistan (Co-PI) vi. Professor Sheila MacNeil, BSc (Hons), PhD Department of Materials Science and Engineering, Emeritus Professor of Biomaterials and Tissue Engineering (Co-PI) vii. Dr. Muhammad Rehan, Post- Graduate Trainee, in Burns and Plastic Surgery, at Burn Care Centre (BCC), Pakistan Institute of Medical Sciences (PIMS), Islamabad. (Co-PI) viii. Zunera Arshad, Research Assistant, Burns Centre, Pakistan Institute of Medical Sciences, Islamabad. (Co-PI) ix. Mohammad Suleman Bajwa, MBBS, MD, Surgery resident (preliminary) - Department of Surgery, Montefiore Medical Center/Albert Einstein College of Medicine (Co-PI) * Roles of above mentioned PI/Co-PIs is not elaborated. Whereas, only one site is mentioned in the application and PI/Co-PIs are from different cities and countries. ** PI of the trial haven't required/mentioned qualification for Clinical Trial Monitoring
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP certificate(s) of following are attached: 1. Licence of M/s Cotton Craft (Pvt.) Ltd, Lahore is attached. (Page 255/Corr.) 2. COA of 2-Deory-Dribose, Thyminose;2-Deory-Deffi ropentose;2-Deory-Darabinose, issued by BIOSYNTH is attached. * GMP Certificate and CoPP are not provided.
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Not provided separately.
16	Summary of Investigator Brochure	Not provided separately.
17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	Phase I: 37 subjects will be enrolled. Phase II: 50 subjects will be enrolled. 3. At once only one phase can be approved.
19	Name of Monitors & Clinical Research Associate	• Dr. Shafiullah • Sehrosh Naz Khan

		• Samreen Fatima • Hamna Ahmed • Ariba Javed * Above mentioned monitors are employees of CBSCR-ICCBS and trial site is ICCBS so employees of the same organization cant monitor the trial at the same site where they are employed
20	Evidence of registration in country of origin.	Not provided.
21	Copy of registration letter (if registered in Pakistan)	Not provided.
22	Sample of label of the investigational product / drug.	Attached but not proper for Clinical Trial.
23	Duration of trial	07 Months
24	Undertaking on Stamp paper	Attached

** ***Quantity of investigational products to be used in the trial along with justification:***
(Note: All the quantities of the investigational product should be procured from one single source)

Investigation al Product *(2 dD R-tulle gras dressing)*

- *Dose: twice a week*
- *Total Week: 12 weeks*
- *Total sheets/patients: 24 sheets*

For Phase I: - (37 patients- 4:4:1, 16:16:5)

➤ *For Normal Dose →Total no. of sheets of 16 patients: 16×24=384 sheets*
Retention samples for archiving (5% of trial requirement): 384/100 x 5 = 19.2 (20 sheets)
Total no. of sheets for normal dose of 16 patients + retention samples for archiving = 384+20=404

➤ *For Placebo Dose →Total no. of sheets of 16 patients: 16×24 = 384 sheets*
Retention samples for archiving (5% of trial requirement): 384/100 x 5 = 19.2 (20 sheets)
Total no. of sheets for placebo dose of 16 patients + retention samples for archiving = 384+20=404

➤ *For Super Normal Dose →Total no. of sheets of 5 patients: 5×24 = 120 sheets*
Retention samples for archiving (5% of trial requirement): 120/100 x 5 = 6 sheets
Total no. of sheets for super normal dose of 5 patients + retention samples for archiving = 120+6 = 126

For Phase II: - (50 patients- 1:1, 25:25)

➤ *For Normal Dose →Total no. of sheets of 25 patients: 25×24 = 600 sheets*
Retention samples for archiving (5% of trial requirement): 600/100 x 5 = 30 sheets
Total no. of sheets for normal dose of 25 patients + retention samples for archiving = 600+30= 630

➤ *For Placebo Dose Total no. of sheets of 25 patients: 25x24 = 600 sheets*
Retention samples for archiving (5% of trial requirement): 600/100 x 5 = 30 sheets
Total no. of sheets for placebo dose of 25 patients + retention samples for archiving = 600+30=630

Total no. of sheets for normal dose: 1034
Total no. of sheets for placebo dose: 1034
Total no. of sheets for super normal dose: 126

NOTE:
Reference of Latest ICH-GCP E6(R2) Guidelines
4.3 Medical Care of Trial Subjects

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.
4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant

laboratory values, related to the trial. The investigator/institution should inform a subject when medical care is needed for inter-current illness(es) of which the investigator becomes aware.
4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

Reference of Guidelines to Conduct Clinical Research in Pakistan.

7.4. Principal Investigator: Principal Investigator (PI) is the researcher, usually a doctor or other healthcare professional, who assumes full responsibility for a research study, including but not limited to, the oversight and training of research assistants, administration of informed consent, and protecting participant confidentiality and leads the clinical research along with the other members of the research team, regularly monitors study participants' health to determine the study's safety and effectiveness. A PI is primarily responsible for the preparation, conduct, and administration of a research grant, cooperative agreement, or other sponsored project in compliance with applicable laws and regulations and institutional policy governing the conduct of clinical research. In case where application is for Clinical Research of Medical Device or Alternate Medicine, a Clinician/Medical Doctor must be the part of the study team or the case may be decided by the CSC.

After initial scrutiny/evaluation following shortcomings has been observed:
* Composition of IRBs of following are not attached.
- King Edward Medical University, Lahore
- Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad

*Monitors are employees of CBSCR-ICCBS and trial site is ICCBS so employees of the same organization can't monitor the trial at the same site where they are employed

*Roles of PI/Co-PIs is not elaborated. Whereas, only one site is mentioned in the application and PI/Co-PIs are from different cities and countries.

* PI of the trial hasn't required/mentioned eligibility (as described by ICH and relevant guidelines) for Clinical Trial Monitoring

4. In order to avoid conflict of interest, the Secretary, CSC (being evaluator of the case) will not participate in voting.

5. The case was presented before the CSC in its 52nd meeting held on 28th November 2024. The Committee decided the case as follows:

Decision: The CSC after deliberation observed that there are a number of shortcomings in the application and decided to defer the case for communication of shortcomings to the applicant as discussed.

6. After detailed evaluation of the application following clarifications are sought by the CSC expert members:

i. Composition of IRBs of following are not attached.
   - King Edward Medical University, Lahore
   - Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad
ii. Monitors are employees of CBSCR-ICCBS and trial site is ICCBS so employees of the same organization can't monitor the trial at the same site where they are employed
iii. Roles of PI/Co-PIs is not elaborated. Whereas, only one site is mentioned in the application and PI/Co-PIs are from different cities and countries.
iv. PI of the trial hasn't required/mentioned eligibility (as described by ICH and relevant guidelines) for Clinical Trial Monitoring
v. The Clinical Trial team is comprised of the following:

a. Plastic surgeon
b. Burn specialist
c. Chemist (but no dialectologist and Pharmacist is included, clarification sought in this regard)

vi. The references provided are too old, latest being from 2019, clarification required.

vii. In the formulation Bees Wax, Petroleum products and cetosteryl alcohol are mentioned but proper drug release study is not provided to confirm the permeation of 2 doxy D ribose from the gauze dressing to the wound. There is a possibility of entry of the drug to systemic circulation that may lead to toxicity.

viii. Majority of the preclinical studies shown in the dossier are conducted by researchers not part of the team related to the development of foot dressing of 2 deoxy D ribose, for example, in the Rat Cutaneous Wound Model conducted by Mac Neil & Yar group (no proper reference given in the dossier). In this study freezed gelated hydrogels is used as a base of the drug which does not correlate with the bases used in the current study.

ix. In some preclinical studies future tense is used that shows that work will be conducted in future i.e. toxicity test, Principal of sensitization test.

x. The photomicrographs and graphs of the preclinical studies are not visible and difficult to read. Further, simple student T-Test is applied to the data where there are multiple groups in the studies.

xi. An ideal DW model should progress toward reprehensibility, quantifiable interpretation, therapeutic significance, and effective translation into clinical use. Proper animal model for the study for diabetic wound healing is the rat and mice models. No systematic in-vivo animal study/studies are available in the dossier to support the clinical trials of the product for the diabetic foot ulcer except:

a. Assessment of wound healing responses to 2 deoxy- D -ribose loaded into freeze gelated hydro-gel using a rat cutaneous wound mode model- non-diabetic animals conducted by Prof MacNeil and Dr. Yar groups in another study where freezed gelated hydrogel is used as a base.
b. In vivo evaluation of effect of 2-dDR on diabetic wound healing in the diabetic rat model was assessed by using a single application of 2- ***dDR-loaded alginate dressings? In this study the alginate dressing is not the one proposed in the study.***

xii. The preparation is meat for healing the diabetic foot ulcer but the diabetic foot healing is not mentioned in the objectives of the study.

xiii. In summary, this study is a collection of difference preclinical reports from different authors to justify the clinical trials of 2 deoxy D ribose for diabetic foot ulcer without proper systematic relevant purposeful preclinical data. It is pertinent to mention that topical dressing can permeate into the tissue and systemic circulation that may cause systemic toxicity.

xiv. Some of the untoward effects of angiogenic drugs are mentioned below:

a. An angiogenic agent will disseminate and induce unintended angiogenesis in adjacent and perhaps even in distant sites.
b. Increased Vascular permeability
c. Induction of the development of functionally abnormal blood vessels
d. **Triggering Growth of Neoplasms:** here is strong evidence that solid tumors require an angiogenic response to supply the nutrients required for growth beyond minimal size. Induction of angiogenesis therefore provides an additional mechanism by which an angiogenic agent administered to treat tissue ischemia could trigger the growth of dormant or in situ tumors independently of any direct effects that the agent might have on tumor cell proliferation.
e. It has been demonstrated experimentally that prolonged exposure of skeletal muscle or myocardium to high local levels of VEGF or FGF family peptides can cause hemangioma like tumors and vascular malformations. Also, certain normal tissues, notably the uterus, possess functional VEGF receptor tyrosine kinases; in fact, VEGF is mitogenic for uterine smooth muscle. It is therefore possible that the common leiomyoma (fibroid) could at least theoretically respond to exogenous stimulation by growth factors.
f. Vasodilatation and Hypotension During Short-Term Administration of FGF and VEGF Proteins.
g. There is a lack of readily available animal models that sufficiently approximate human diabetic wound healing, especially chronic wounds. Moreover, many of the preclinical animal studies to date have focused on monotherapies, an approach which seems unlikely to be adequate for the treatment of the multifactorial problem of diabetic chronic skin wounds.

6. The case was placed before the Committee for information and consideration. The Committee decided the case as under:

Decision: The CSC after deliberation decided to defer the case for submission of clarification regarding following shortcomings:

i. Composition of IRBs of following are not attached.
   - King Edward Medical University, Lahore.
   - Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad.

ii. Monitors are employees of CBSCR-ICCBS and trial site is ICCBS, employees of the same organization can't monitor the trial at the same site where they are employed

iii. Roles of PI/Co-PIs is not elaborated. Whereas, only one site is mentioned in the application and PI/Co-PIs are from different cities and countries.

iv. PI of the trial does not have the required/mentioned eligibility (as described by ICH and relevant guidelines) for Clinical Trial Monitoring.

v. The Clinical Trial team does not include any dialectologist and pharmacist.

vi. The references provided are from 2019 ante, latest references may also be provided.

vii. Bees wax, petroleum products and cetosteryl alcohol are mentioned in the formulation but proper drug release study has not been provided to confirm the permeation of 2 doxy D ribose from the gauze dressing to the wound. There is a possibility of entry of the drug to systemic circulation that may lead to toxicity.

viii. Majority of the preclinical studies shown in the dossier are conducted by researchers not part of the team related to the development of foot dressing of 2 deoxy D ribose, for example, in the Rat Cutaneous Wound Model conducted by Mac Neil & Yar group (no proper reference given in the dossier). In this study freezed gelated hydrogels is used as a base of the drug which does not correlate with the bases used in the current study.

ix. In some preclinical studies future tense is used that shows that work will be conducted in future i.e. toxicity test, principal of sensitization test.

x. The photomicrographs and graphs of the preclinical studies are not visible and difficult to read. Further, simple student T-Test is applied to the data where there are multiple groups in the studies.

xi. An ideal DW model should progress toward reprehensibility, quantifiable interpretation, therapeutic significance, and effective translation into clinical use. Proper animal model for the study for diabetic wound healing is the rat and mice models. No systematic in-vivo animal study/studies are available in the dossier to support the clinical trials of the product for the diabetic foot ulcer except:

   a. Assessment of wound healing responses to 2 deoxy- D -ribose loaded into freeze gelated hydro-gel using a rat cutaneous wound mode model- non-diabetic animals conducted by Prof MacNeil and Dr. Yar groups in another study where freezed gelated hydrogel is used as a base.
   b. In vivo evaluation of effect of 2-dDR on diabetic wound healing in the diabetic rat model was assessed by using a single application of 2- *dDR-loaded alginate dressings, whereas, in this study alginate dressing is not proposed.*

xii. Apparently the preparation is meant for healing the diabetic foot ulcer whereas the diabetic foot healing is not mentioned in the objectives of the study.

xiii. Topical dressing can permeate into the tissue and systemic circulation that may cause systemic toxicity. Evidence of clinical safety regarding the following possible untoward effects of angiogenic drugs may be provided:
   a. An angiogenic agent will disseminate and induce unintended angiogenesis in adjacent and perhaps even in distant sites.
   b. Increased Vascular permeability
   c. Induction of the development of functionally abnormal blood vessels
   d. Triggering Growth of Neoplasms: here is strong evidence that solid tumors require an angiogenic response to supply the nutrients required for growth beyond minimal size. Induction of angiogenesis therefore provides an additional mechanism by which an angiogenic agent administered to treat tissue ischemia could trigger the growth of dormant or in situ tumors independently of any direct effects that the agent might have on tumor cell proliferation.
   e. It has been demonstrated experimentally that prolonged exposure of skeletal muscle or myocardium to high local levels of VEGF or FGF family peptides can cause hemangioma like tumors and vascular malformations. Also, certain normal tissues, notably the uterus, possess functional VEGF receptor tyrosine kinases; in fact, VEGF is mitogenic for uterine smooth

muscle. It is therefore possible that the common leiomyoma (fibroid) could at least theoretically respond to exogenous stimulation by growth factors.

f. Vasodilatation and Hypotension During Short-Term Administration of FGF and VEGF Proteins.

xiv. There is a lack of readily available animal models that sufficiently approximate human diabetic wound healing, especially chronic wounds. Moreover, many of the preclinical animal studies to date have focused on monotherapies, an approach which seems unlikely to be adequate for the treatment of the multifactorial problem of diabetic chronic skin wounds.

xv. The IMP need to be manufactured in GMP compliant facility, clarification in this regard is required.

07. Accordingly, the CSC decision was communicated to applicant vide letter No. 16-53/2024-CT dated 09th January 2025, yet response is awaited.

08. The case was placed before the Committee for consideration. The Committee decided the case as under:

Decision: The CSC after deliberation decided to defer the case for submission of clarification regarding following shortcomings (already communicated on 09th January 2025:):

i. **Composition of IRBs of following are not attached.**
   - **King Edward Medical University, Lahore.**
   - **Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad.**

ii. **Monitors are employees of CBSCR-ICCBS and trial site is ICCBS, employees of the same organization can't monitor the trial at the same site where they are employed**

iii. **Roles of PI/Co-PIs is not elaborated. Whereas, only one site is mentioned in the application and PI/Co-PIs are from different cities and countries.**

iv. **PI of the trial does not have the required/mentioned eligibility (as described by ICH and relevant guidelines) for Clinical Trial Monitoring.**

v. **The Clinical Trial team does not include any dialectologist and pharmacist.**

vi. **The references provided are from 2019 ante, latest references may also be provided.**

vii. **Bees wax, petroleum products and cetosteryl alcohol are mentioned in the formulation but proper drug release study has not been provided to confirm the permeation of 2 doxy D ribose from the gauze dressing to the wound. There is a possibility of entry of the drug to systemic circulation that may lead to toxicity.**

viii. **Majority of the preclinical studies shown in the dossier are conducted by researchers not part of the team related to the development of foot dressing of 2 deoxy D ribose, for example, in the Rat Cutaneous Wound Model conducted by Mac Neil & Yar group (no proper reference given in the dossier). In this study freezed gelated hydrogels is used as a base of the drug which does not correlate with the bases used in the current study.**

ix. **In some preclinical studies future tense is used that shows that work will be conducted in future i.e. toxicity test, principal of sensitization test.**

x. **The photomicrographs and graphs of the preclinical studies are not visible and difficult to read. Further, simple student T-Test is applied to the data where there are multiple groups in the studies.**

xi. **An ideal DW model should progress toward reprehensibility, quantifiable interpretation, therapeutic significance, and effective translation into clinical use. Proper animal model for the study for diabetic wound healing is the rat and mice models. No systematic in-vivo animal study/studies are available in the dossier to support the clinical trials of the product for the diabetic foot ulcer except:**

   a. **Assessment of wound healing responses to 2 deoxy- D -ribose loaded into freeze gelated hydro-gel using a rat cutaneous wound mode model- non-diabetic animals conducted by Prof MacNeil and Dr. Yar groups in another study where freezed gelated hydrogel is used as a base.**
   b. **In vivo evaluation of effect of 2-dDR on diabetic wound healing in the diabetic rat model was assessed by using a single application of 2- *dDR-loaded alginate dressings, whereas, in this study alginate dressing is not proposed.***

xii. **Apparently the preparation is meant for healing the diabetic foot ulcer whereas the diabetic foot healing is not mentioned in the objectives of the study.**

xiii. **Topical dressing can permeate into the tissue and systemic circulation that may cause systemic toxicity. Evidence of clinical safety regarding the following possible untoward effects of angiogenic drugs may be provided:**

a. **An angiogenic agent will disseminate and induce unintended angiogenesis in adjacent and perhaps even in distant sites.**
b. **Increased Vascular permeability**
c. **Induction of the development of functionally abnormal blood vessels**
d. **Triggering Growth of Neoplasms: here is strong evidence that solid tumors require an angiogenic response to supply the nutrients required for growth beyond minimal size. Induction of angiogenesis therefore provides an additional mechanism by which an angiogenic agent administered to treat tissue ischemia could trigger the growth of dormant or in situ tumors independently of any direct effects that the agent might have on tumor cell proliferation.**
e. **It has been demonstrated experimentally that prolonged exposure of skeletal muscle or myocardium to high local levels of VEGF or FGF family peptides can cause hemangioma like tumors and vascular malformations. Also, certain normal tissues, notably the uterus, possess functional VEGF receptor tyrosine kinases; in fact, VEGF is mitogenic for uterine smooth muscle. It is therefore possible that the common leiomyoma (fibroid) could at least theoretically respond to exogenous stimulation by growth factors.**
f. **Vasodilatation and Hypotension During Short-Term Administration of FGF and VEGF Proteins.**

xiv. **There is a lack of readily available animal models that sufficiently approximate human diabetic wound healing, especially chronic wounds. Moreover, many of the preclinical animal studies to date have focused on monotherapies, an approach which seems unlikely to be adequate for the treatment of the multifactorial problem of diabetic chronic skin wounds.**

xv. **The IMP need to be manufactured in GMP compliant facility, clarification in this regard is required.**

2. Further it is decided to inform PI that fulfill all prerequisite within a month positively for further processing of the application.

09. Accordingly, the CSC Decision was communicated on 04th February 2025, yet response is awaited.

10. Application was placed before the 55th CSC Meeting, the Committee decided as follows:

Decision: The CSC after deliberation decided to defer the case for fulfilment of shortcomings, communicated on vide letter 04th February, 2025.

11. The PI vide letter reference No. nil dated 19th March, 2025 responded to the shortcomings/ observations which were communicated by this office vide letter F. No. 16-53/2024 CSC on 09/01/2025. The response is presented below: -

(In order to avoid conflict of interest, the Secretary, CSC (being evaluator of the case) will not participate in voting.)

CSC's Comment-1: Composition of IRBs of following are not attached • King Edward Medical University, Lahore • Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad
PI Response: The composition of IRB of King Edward Medical University, Lahore and Shaheed Zulfiqar Ali Bhutto Medical University, Islamabad are attached. ***(Annexure 1)***
CSC's Comment-2: Monitors are employees of CBSCR-ICCBS and trial site is ICCBS, employees of the same organization can't monitor the trial at the same site where they are employed.
PI Response: Dr. Shafiullah will be the monitor and he is currently serving as an Associate Professor, at the Faculty of Pharmaceutical Sciences, Superior University, Lahore, Punjab, Pakistan from October 2023.
CSC's Comment-3: Roles of PI/Co-PIs is not elaborated. Whereas, only one site is mentioned in the application and PI/Co-PIs are

from different cities and countries.

PI Response:

This is an opportunity for us to apologize for not having made this clear and to give some dialogue describing the roles of the PI/Co-PIs.;

As a principle Investigator of the study, the role of Dr. Raza Shah is:

- Compilation and Submission of regulatory dossier
- Overall conduct of the study
- Training of staff for clinical study
- Ensuring double blindness of the study
- Supervising and ensuring randomization of patients participating in the study
- Look after writing of protocol and report

Emeritus Prof Sheila MacNeil is a Co-PI on this application based on her long history of collaborating with Prof. Yar and her experience of translating research to the clinic in the UK and India. She and Prof. Yar have played leading roles in assembling a clinical team in Pakistan who are committed to developing low-cost, effective treatments for patients in Pakistan. Prof. MacNeil uses her extensive experience of translational research to help guide this new study to take place in Pakistan safely and with full regulatory approval. Prof. Yar is the lead academic for this project receiving support on clinical matters from Prof. Mustehsan Bashir Head Burn unit KEMU and Prof. Tariq Iqbal Head burn unit PIMS Islamabad and on regulatory approval from Prof. Raza Shah CBSRC Karachi University. The team assembled for this project have worked together productively since its inception and are now looking forward to taking it into the clinic once for approval is received from DRAP etc.

Thank you for your observation. The submitted application specifies a single site that is ***Center for Bioequivalence Studies and Clinical Research, International Center for Chemical and Biological Sciences (ICCBS), University of Karachi,*** for the trial's primary activities, while the Co-PIs are from different cities of Pakistan (Islamabad and Lahore) and their sites will work as collaborative organizations. The collaborative nature of the research allows team members to contribute remotely, leveraging their respective expertise.

CSC's Comment-4:

PI of the trial does not have the required/mentioned eligibility (as described by ICH and the relevant guidelines) for Clinical Trial Monitoring.

PI Response:

The PI of this trial, Prof. Dr. M. Raza Shah has extensive experience in DRAP and NBC-approved clinical trials including clinical trials of COVID-19. The PI of this study led the DRAP and NBC approved Phase I clinical trial of the Sinopharm Vaccine in Pakistan and successfully completed. The followings are the credentials of PI related to Clinical Research:

1. The PI of this trial remained as PI of DRAP and NBC approved Clinical Trial for the treatment of COVID-19 patients with Traditional Chinese Medicine, entitled "Multi-center, Randomized, Double Blind and Placebo Controlled Clinical Trial on the Efficacy and Safety of Jinhua Qinggan Granules (JHQG) for the Treatment of COVID-19 Patients". The trial is successfully completed and the results of the trial are published in leading international journal of high impact factor. ***(Annexure 2: NBC approval, DRAP approval, Publication)***
2. The PI of this trial also remained PI the DRAP and NBC-approved clinical trial entitled "A Randomized, Double-blind, Positive-Controlled Study to Evaluate the Efficacy and Safety of Fuke Qianjin Capsule in Patients with Pelvic Inflammatory Diseases". ***(Annexure 3: NBC approval, DRAP approval, Publication)***
3. The PI of this study also remained PI of the DRAP and NBC-approved clinical trial entitled "Randomized, Double-Blind, Placebo-Controlled, Non-inferiority Clinical Trial on the Efficacy and Safety of Houtou Jianweiling Tablet in the Treatment of Chronic Non-Atrophic Gastritis." ***(Annexure 4: NBC approval, DRAP approval, Publication)***
4. The PI of this study is also acting as PI of NBC approved Phase 1 clinical trial entitled "A single Center, Placebo-Controlled, Ascending Single-Dose Phase 1 Clinical Trial to Evaluate Safety, Tolerability and Pharmacokinetics of RHN-001 in Healthy adult volunteers". ***(Annexure 5: NBC approval, DRAP approval)***
5. The PI of this study has conducted more than 28 Bioequivalence and PK studies in healthy volunteers. The Bioequivalence (BE) studies are a type of Phase 1 clinical trial. In BE (Safety, Pharmacokinetic) studies comparative Safety and Pharmacokinetic of drug is evaluated in health volunteers. All the parameters that are needed for execution of Phase 1 (Safety, Pharmacokinetic, dose tolerability) clinical trial are practiced in true spirit in BE studies. A wealth of knowledge about the clinical trial can be gathered by conducting BE studies. GCP and GLP are practiced both in BE and Phase 1 studies of IND. ***(Annexure 6: List of BA/BE, PK studies and approvals conducted by PI)***
6. The PI of this study has participated in several GCP and GLP training courses needed to act as PI. ***(Annexure 7: Training certificates of PI)***
7. The PI of this study has published more than 200 research articles in the area of Drug Delivery and Nanomedicine through which the PI has gathered a wealth of knowledge about the clinical trials and interactions of the drugs with the human body and the response of the human body to Drug. ***(Annexure 8:***

List of publications in Drug Delivery Therapeutic)

8. The PI of this study has also Published (with International Publisher Elsevier) five books in the area of Drug delivery which increased in the depth of understanding of PI about the drug interaction with the body and response of the body. The books are also available on Amazon and one of the books was declared the best book of the year (2017) by HEC. The title of the books is given below;
   i. Lipid-Based Nanocarriers for Drug Delivery and Diagnosis, **Paperback ISBN: 9780323527293**
   ii. Nanocarriers for Cancer Diagnosis and Targeted Chemotherapy, **Paperback ISBN: 9780128167731**
   iii. Metal Nanoparticles for Drug Delivery and Diagnostic Applications, **Paperback ISBN: 9780128169605**
   iv. Nanocarriers for Organ-Specific and Localized Drug Delivery **Paperback ISBN: 9780128210932**
   v. Stimuli-Responsive Nanocarriers for Targeted Drug Delivery **Paperback ISBN: 9780443223891**
9. The PI of the study also remained as Member in the panel of inspectors for Evaluation of Clinical Trial Sites from Drug Regulatory Authority of Pakistan (DRAP). ***(Annexure 9: Letters received from DRAP to act as inspector)***

Conducted 10 Toxicological Studies, 28 Phase-I Clinical Trials (BE and PK studies) along with 04 Phase-II Clinical Trials (Safety and Efficacy evaluation) for Multinational Pharma Companies as Principal Investigator.

CSC's Comment-5:
The Clinical Trial team does not include any dialectologist and pharmacist.

PI Response:
An endocrinologist Dr. Mammona Gias Assistant Professor at King Edward Medical University Lahore, is included in team who is certified in the clinical setup to medically take care of diabetic patients. We are attaching her CV as a reference. ***(Annexure 10: CV)***

CSC's Comment-6:
The reference provide are from 2019 ante, latest references may also provide.

PI Response:
Here we are providing all of our published papers references on 2-deoxy-D-ribose;

1. Yar, M., Shahzadi, L., Mehmood, A., Raheem, M.I., Roman, S., Chaudhry, A.A., ur Rehman, I., Douglas, C.I. and MacNeil, S., Deoxy-sugar releasing biodegradable hydrogels promote angiogenesis and stimulate wound healing. Materials Today Communications, 2017. 13, pp.295-305.

2.Azam, M., Dikici, S., Roman, S., Mehmood, A., Chaudhry, A.A., U Rehman, I., MacNeil, S. and Yar, M.,Addition of 2-deoxy-d-ribose to clinically used alginate dressings stimulates angiogenesis and accelerates wound healing in diabetic rats. Journal of biomaterials applications, 2019. 34(4), pp.463-475.

3.Dikici, S., Mangır, N., Claeyssens, F., Yar, M. and MacNeil, S., Exploration of 2-deoxy-D-ribose and 17β-Estradiol as alternatives to exogenous VEGF to promote angiogenesis in tissue-engineered constructs. Regenerative medicine, 2019. 14(3), pp.179-197.

4. Andleeb A, Dikici S, Waris TS, et al. Developing affordable and accessible pro-angiogenic wound dressings; incorporation of 2 deoxy D-ribose (2dDR) into cotton fibres and wax-coated cotton fibres. J Tissue Eng Regen Med. 2020; 14: 973–988.

5. Dikici, S., Bullock, A. J., Yar, M., Claeyssens, F., & MacNeil, S. 2-deoxy-d-ribose (2dDR) upregulates vascular endothelial growth factor (VEGF) and stimulates angiogenesis. Microvascular Research, 2020. 131, 104035.

6. Dikici, S., Yar, M., Bullock, A. J., Shepherd, J., Roman, S., & MacNeil, S. Developing Wound Dressings Using 2-deoxy-D-Ribose to Induce Angiogenesis as a Backdoor Route for Stimulating the Production of Vascular Endothelial Growth Factor. International Journal of Molecular Sciences, 2021. 22(21), 11437.

7. Abid S, Zulfiqar S, Anjum MA, Bullock AJ, MacNeil S, Yar M. An alginate-Based tube gel delivering 2-deoxy-D-ribose for stimulation of wound healing. Journal of Biomaterials Applications. 2023;38(2):264-279.

CSC's Comment-7:
Bees wax, petroleum products and cetostearyl alcohol are mentioned in the formulation but proper drug release study has not been provided to confirm the permeation of 2 deoxy D-ribose from the gauze dressing to the wound. There is a possibility of entry of the drug to systemic circulation that may lead to toxicity.

PI Response:
Over the years we have demonstrated that the sugar can be released from a variety of carriers when it came to choosing a carrier for development of a project for treatment of diabetic ulcers. We selected wax coated cotton dressings because they were already being used in Pakistan and we had an excellent, Pakistan-based company to work with-Cotton Craft. We worked with Cotton Craft to develop a delivery system that ensured that a sufficient quantity of sugar was released over several days in conducting this study, we looked at release of the sugar from plain cotton fibers and from wax coated cotton fibers and ended up modifying the composition of the

wax slightly to ensure release of sufficient sugar. This was published in this article; (*Andleeb A, Dikici S, Waris TS, et al. Developing affordable and accessible pro-angiogenic wound dressings; incorporation of 2 deoxy D-ribose (2dDR) into cotton fibers and wax-coated cotton fibers. J Tissue Eng. Regen Med. 2020; 14: 973–988.)*
We were confident of the amount of sugar that needed to be released over a day to achieve stimulation of angiogenesis based on several in vitro studies we have conducted and reported in this article;

(Dikici S, Aldemir Dikici B, Bhaloo SI, Balcells M, Edelman ER, MacNeil S, Reilly GC, Sherborne C and Claeyssens F (2020) Assessment of the Angiogenic Potential of 2-Deoxy-D-Ribose Using a Novel in vitro 3D Dynamic Model in Comparison with Established In vitro Assays. Front. Bioeng. Biotechnol. 7:451.)

It was our intention not to change composition of this wax coated cotton-based fiber product which has been used in Pakistan for the treatment of burns and other injuries for at least 20 years.
The second point, the reviewers raise possibility of entry of the drug to systemic circulation that may lead to toxicity-again. We conducted dose-response studies to the sugar to determine the range of concentrations of sugar that were stimulated angiogenesis and whether there was indeed a toxic dose that could be reached.

On the basis of this we found the effective stimulatory response to be in the range of to be, but concentrations greater than actually inhibited cell proliferation.
Mindful of the need to ensure the safety of the sugar. We conducted toxicity testing experiments in animals and deliberately provided higher concentrations up to 15000mg/kg and results showed that all animals survived, and no sign of organ toxicity observed that depicted systematic safety of the drug. ***(Annexure 11: Report is attached)***

CSC's Comment-8:
Majority of the preclinical studies shown in the dossier are conducted by researchers not part of the team related to the development of the foot dressing of 2 deoxy D ribose, for example, in the Rat Cutaneous Wound Model conducted by Mac Neil & Yar group (no proper reference given in the dossier). In this study freezed gelated hydrogels is used as a base of the drug which does not correlate with the bases used in the current study.

PI Response:
As part of our collaboration, we have explored delivery of the sugar from a variety of carriers including hydrogels. The sugar could be successfully delivered from a hydrogel, and we established that the sugar stimulated angiogenesis in wounds in a rat cutaneous wound model.

(*Yar, M., Shahzadi, L., Mehmood, A., Raheem, M.I., Roman, S., Chaudhry, A.A., ur Rehman, I., Douglas, C.I. and MacNeil, S., Deoxy-sugar releasing biodegradable hydrogels promote angiogenesis and stimulate wound healing. Materials Today Communications, 2017. 13, pp.295-305.)*

We agree this hydrogel is not the material to be used in the current study- we changed to using a wax coated cotton dressing because this was already addressing widely accepted for clinical use in Pakistan and we had a commercial partner who was keen to develop this with us.

CSC's Comment-9:
In Some preclinical studies future tense is used that shows the work will be conducted in future i.e. toxicity test, principal of sensitization test.

PI Response:
We apologize for talking about tests to be completed in the future. All tests have been completed and correction has been done in the report.

CSC's Comment-10:
The photomicrographs and graphs of the preclinical studies are not visible and difficult to read. Further, simple student T-Test is applied to the data where there are multiple groups in the studies.

PI Response:
We have attached much larger photomicrographs and graphs of the preclinical studies we have now subjected the data to slightly more sophisticated statistics suitable for use of multiple groups, and these results are attached in Annexure 11. ***(Annexure 12: Larger photomicrographs)***

CSC's Comment-11:
An ideal DW model should progress toward reprehensibility, quantifiable interpretation, therapeutic significance,

and effective translation into clinical use. Proper animal model for the study for diabetic wound healing is the rat and mice models. No systematic in-vivo animal study/studies are available in the dossier to support the clinical trials of the product for the diabetic foot ulcer except.

a. *Assessment of wound healing responses to 2-deoxy-D-ribose loaded into freeze gelated hydro-gel using a rat cutaneous wound mode model, non-diabetic animals conducted by Prof MacNeil and Dr. Your groups in another study where freezed gelated hydrogel is use as a base.*
b. *In vivo evaluation of effect of 2-dDR on diabetic wound healing in the diabetic rat model was assessed by using a single application of 2-dDr-loaded alginate dressings, whereas, in this study alginate dressing is not proposed.*

PI Response:

We agree that it's very difficult to find an animal model that reproduces the complexity of diabetic wounds when we made our initial observation that the sugar stimulated wound healing. It was on a healthy rat model with their full thickness cutaneous wound.

Aware that this does not mimic the problems of diabetes. We then went on to establish a diabetic wound healing model and delivered the sugar using alginate dressings-this preceded are developing a relationship with Cotton Craft to take this work to the clinic.

We did consider using alginate dressing, but when it came down to designing the study. We felt there was a compelling argument to be made use addressing that already existed in Pakistan had been produced under drug approved conditions and was well accepted by clinicians, especially as it gave us the opportunity of working with a Pakistan-based company to develop a low-cost dressing to benefit patients in Pakistan.

CSC's Comment-12:

Apparently, the preparation is meant for healing the diabetic foot ulcer whereas the diabetic foot healing is not mentioned in the objectives of the study.

PI Response:

Clarification on Study Objectives

We would like to clarify that this study specifically investigates the healing of diabetic foot ulcers using 2dDR-tulle gras dressing compared to a placebo-control dressing.

The primary objective is to assess the safety, tolerability, and effects of 2dDR-tulle gras dressing compared to a placebo-control dressing in the context of diabetic foot ulcer healing.

The secondary objectives further explore:

- The incidence of complete healing and 40% wound healing in DFUs.
- Cost-effectiveness of the treatment arms.
- Effects on wound-related quality of life in patients with DFUs.
- Dressing properties, including ease of application, complications (e.g., allergic response, bleeding, granulation quality, malodor, leaks, unexpected re-dressing), and patient compliance.

While the term "diabetic foot ulcer" was not explicitly stated in the objectives, the study is indeed focused on assessing the healing of DFUs.

CSC's Comment-13:

Topical dressing can permeate into the tissue and systemic circulation that may cause systemic toxicity. Evidence of clinical safety regarding the following possible untoward effects of angiogenic drugs may be provided:

a. An angiogenic agent will disseminate and induce unintended angiogenesis in adjacent and perhaps even in distant sites.
b. Increased Vascular Permeability
c. Induction of the development of functionally abnormal blood vessels
d. Triggering Growth of Neoplasms, here is strong evidence that solid tumors require an angiogenic response to supply the nutrients required for growth beyond minimal size. Induction of angiogenesis therefore provides an additional mechanism by which an angiogenic agent administered to treat tissue ischemia could trigger the growth of dormant or in situ tumors independently of any direct effects that the agent might have on tumor cell proliferation.
e. It has been demonstrated experimentally that prolonged exposure of skeletal muscle or myocardium to high local levels of VEGF or FGF family peptides can cause hemangioma like tumors and vascular malformations. Also, certain normal tissues, notably the uterus, possess functional VEGF receptor tyrosine kinases; in fact, VEGF is mitogenic for uterine smooth muscles. It is therefore possible that the common leiomyoma (fibroid) could at least theoretically respond to exogenous stimulation by growth factors.
f. Vasodilation and Hypotension During Short-Term Administration of FGF and VEGF Proteins.

PI Response:

We are very much aware of the suspension of clinical studies using topical applications of VEGF. In hindsight, it appears that this response of large leaky vessels was due to the delivery of large unregulated concentrations of VEGF.

We have established that the sugar leads up to regulation (temporarily) of VEGF. Also, we have undertaken extensive toxicity testing and have not found any evidence of adverse responses to the delivery of the sugar.

CSC's Comment-14: There is a lack of readily available animal models that sufficiently approximate human diabetic wound healing, especially chronic wounds. Moreover, many of the preclinical animal studies to date have focused on monotherapies, an approach which seems unlikely to be adequate for the treatment of the multifactorial problem of diabetic chronic skin wounds.
PI Response: We agree there is a lack of readily available animal models that approximate human diabetic wound healing. We suggest the approach we are proposing that of up regulating angiogenesis is a sensible approach to tackle poor wound healing in diabetics where the blood vessels are quite commonly compromised and is worthy of careful investigation.
CSC's Comment-15: The IMP need to be manufactured in GMP compliant facility, clarification in this regard is required."
PI Response: We are providing details of the manufacture of the cotton dressing containing sugar by Cotton Craft in a GMP compliant facility. cGMP certificate was provided with the application. All the dressings used in this project have been prepared in the cGMP facility of the Cotton Craft. ***(Annexure 13: Manufacturing License)***

12. The case was placed before the CSC for consideration.

Decision: The CSC after consideration decided to defer the case for further deliberations.

13. The case was placed before the CSC for consideration.

Proceedings:

Prof. Dr. Raza Shah (Ph.D. Organic Chemistry), Director, ICCBS, University of Karachi, Karachi, joined the meeting through Zoom link and explained the trial design, technical aspects of the study. The CSC members commented on the establishment of clinical equipoise for the Phase-I clinical trial since this is a placebo controlled trial. The PI responded that placebo controlled group will receive unmediated tulle gras with a secondary dressing of a layer of fluffy cotton gauze (approximately 2cm thick) covered in a layer of cling film. The expert members of CSC (clinicians) opined that the DFA being a complication of uncontrolled diabetes can pose a potential threat to the subjects if prompt management with topical antibiotics/ antiseptics is evaded or delayed. Furthermore, the PI stated that in case a subject enrolled in the placebo –controlled group develops some complication (wound management) he/she will be managed promptly.

14. The Committee decided the case as under:

Decision:

The CSC after deliberation decided to reject the Clinical Trial titled, "A Multicenter, Double-Blind, Randomized, Placebo-Controlled, 2-Arm Mixed Phase 1 / 2 Clinical Trial to Evaluate the Effects of 2 Deoxy Ribose on Healing of Chronic Diabetic Foot Ulcers", due to following reasons:

i. **The applicant couldn't justify the establishment of Clinical equipoise where the controlled arm will be administered a placebo bandage (without medication)**
ii. **None of the proposed site(s) are licensed to act as Clinical Trial Sites for Phase-I/II Clinical Trials**
iii. **M/s Cotton Craft is holding establishment licence (ELM-0015) for manufacturing of registered product (Surgical Tulle Dressing Section). Whereas, approval of the MDB/Concerned Authority for production of IMP has not be provided.**
iv. **The applicant is not qualifying the criteria as prescribed in the "Guidelines for Conduct of Clinical Research in Pakistan", made under the Bio-Study, 2017.**
v. **The response of the PI to the queries of the CSC, communicated vide letter bearing F. No. 16-53/2024 CSC, dated 09/01/2025 was not found satisfactory by the Committee.**

CASE No. 3.5:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED, "AN OPEN-LABEL, RANDOMIZED, POSITIVE-CONTROLLED, PHASE-I/II CLINICAL TRIAL TO EVALUATE THE SAFETY AND EFFICACY OF PVA TAPIOCA PEARL STARCH-BASED HYDROGEL IN ENHANCING THE HEALING OF BURN WOUNDS" FROM CBSCR-ICCBS, KARACHI.F. No.03-61/2024-CT (PS)

Application on the prescribed form along with fee is received from Prof. Dr. Raza Shah PI of the trial, for registration of the above mentioned Phase I-II clinical trial at the International Center for Chemical and Biological Sciences, Karachi.

Name of Active Ingredient(s): *PVA Tapioca Pearl Starch-Based Hydrogel + Curcumin*
Study Title: *"An open label, randomized. positive-controlled, phase-1111 clinical trial to evaluate the safety and efficacy of PVA Tapioca Pearl Starch-Based Hydrogel in enhancing the healing cl bum wounds."*
Study Duration: *Approximately 3 weeks.* ***Sample Size:*** *Phase I: 36 patients will be enrolled.* *Phase II: 50 patients will be enrolled.*
Study Objectives for Phase I/II: *Primary objective(s): To evaluate the safety and efficacy of PVA Tapioca Pearl Starch-Based hydrogel + Curcumin to positive-controlled dressing 3MTM Tegadcm1TM Hydrocolloid Dressing/Sofratulle.* ***Secondary objective(s):*** *To compare the incidence of adverse events in patients treated with PV A tapioca pearl starch-based hydrogel + Curcumin versus positive control dressing i.e. 3M™ Tegaderm ™ Hydrocolloid Dressing/Sofratulle as determined by the proportion of patients who experience adverse events.*
Study Design: *The study includes a Phase I part and a Phase II part.* *Treatment Duration: The treatment duration for eligible patients is 2 weeks or until complete re-epithelialization of wound occurs. Eligible patients will be randomized and follow up will be taken after 1 week of intervention.* *Patients will be randomized into two groups i.e. treatment group i.e. PVA Tapioca Pearl Starch-Based Hydrogel + Curcumin and positive-controlled i.e. 3;\fTM TegadermTM 1-fydrocol/oid dressing/ S({(ratulle group in a ratio of 1:1.* *A meeting of DSMB will be held to evaluate the safety of the Phase-I clinical trial after 14 day of treatment of the last subject (i.e. 36 subject) enrolled in the trial. Therealler, the DSMB will submit their recommendations for the initiation of recruitment of Phase-II clinical trial to PI. After receiving recommendation from the DSMB, the PI will initiate the recruitment of the subjects in Phase 11 clinical trial.* ***Housing:*** *There will no housing of the patients in this trial.* *a) Treatment Group* *Test Product, Dose and lYfode of Administration and duration:* *PVA Tapioca Pearl Starch-Based Hydrogel + Curcumi11* *Mode of administration: One sheet topically applied as a dressing, once daily. a dressing will be applied for at least* *6-8 hours/day.* *a) Sheet dressings typically can be cut to fit the wound.* *b) Positive-controlled Group* *JMTM Tegaderm™ l(vdrocol/oid Dressing/ Sofratulle* *Mode of administration: Dressing will be applied on burn wound site (at least 6-8 hours/ day).* *o Sheet dressings typically can be cut to fit the wound.*
Criteria for Inclusion: *1. Age 18 years or older* *2. Superficial or partial thickness burn (2m1 degree wound) with individual confluent areas< 15%*

(determined by "Lund Browder Chart". the "Rule of Nines", or the "Rule of Palms). *3. There is no evidence of any other co-morbid condition in the patients.* *4. Patient has signed the informed consent form*
Criteria for Exclusion: *(1) Target wound has exposed hyalinc cartilage* *(2) Burn wounds in the axillary or inguinal region, deep body folds, or a distinctive adipose tissue region* *(3) Connective tissue disorder* *(4) Total bum surface area> 15%* *(5) Infected target wound* *(6) Burns caused by chemicals. electricity or radiation* *(7) Chronic hemodialysis* *(8) Steroid use* *(9) Diabetes (Type f)* *(10) Patients with known allergies to product containing aluminum, hydrogel or a history of contact dermatitis* *(11) Treated with other agents before attend to clinic (oil. tooth paste. betadine. riv,mol, etc.)* *(12) Simultaneous participation in another clinical trial*
Sample Collection: *Wound secretion or exudate samples will be collected for bacterial culture.*
Criteria for Evaluation: *The safety evaluation will be based on the assessment of reported adverse events. Primary Outcome Measures:* *Wound healing [Time Frame: Up to 3 weeks]* *Wound healing as determine by the time of complete re-epithelization of the study area. Secondary Outcome Measures:* • *Erythema [Time Frame: at the time of admission up to 3 0 minutes]* *The presence of erythema* • *Pain score [Time Frame: at the time of admission up to 30 minutes and pt. week of follow-up] Pain score is determined by VAS score (1 - 1 0, 1 is no pain 10 is severe pain).* • *Adverse events [Time Frame: At the time of admission up to 3 weeks of follow ups]* *The adverse events in patients treated with PVA tapioca pearl starch-based hydrogel + Curcumin versus positive control dressing i.e. 3AJTM Tegadem1TM Hydroco/loid Dressing1Sofra11tlle as determined by the proportion of patients who experience adverse events1*
Statistical Methods: *The Statistical Package for Social Sciences (SPSS) will be used to analyze data. Quantitative variables will be expressed as mean± standard deviation/ median (!QR) and qualitative variables as frequencies (percentages). The efficacy and safety will be assessed by intention to treat analysis (ITT). The p-value of less than 0.05 will be considered statistically significant.* *For incidence of healing. logistic regression will be used. The estimated effect size is given as an odds ratio (OR) with confidence intervals (CI).* *Drug safety (SAE/AE) will be assessed by stratified analysis. The incidence of adverse event□ and changes in management plan will be analyzed by Chi-square test.* *Simple regression analysis will be used for adjustment for the confounding variables.* *Sample size:* *Keeping the alpha of 0.05, beta of0.2, and a power of0. 8, the sample size for each phase is as follows;* *Phase-I: The sample size in Phase-1 for each arm required is 16 patients, with 32 patients in total. Accounting for an estimated dropout rate of 10%. the total sample size would be of 35 patients. Rounding to an even number, the sample size for the intervention and control groups becomes 36 (18+ 18).* *Phase-2: The sample size in phase-2 for each arm required is 22 patients, with 44 patients in total. Accounting for an estimated dropout rate of 10%. the total sample size would be of49 patients. Rounding to an even number, the sample size for the intervention and control groups becomes 50 (25+25).*

6. The case was placed before the Committee for consideration. The Committee decided the case as under:

Decision: The CSC after deliberation and discussion decided to defer the case for complete evaluation.

7. Accordingly, the CSC decision was communicated to applicant vide letter No. 16-53/2024-CT dated 09th January 2025.

Remarks by CSC Expert Members
1. **Inconsistency in the Name of the Investigational Product (IP):** The name of the investigational product (IP) appears inconsistently across different sections of the

protocol and related documents. For example, some sections refer to it as "PVA Tapioca Pearl Starch-Based Hydrogel," while others include "Curcumin" as part of the name. This inconsistency may cause confusion and impact the clarity of the study documentation. Ensure that the IP is referred to using a standardized and consistent name across all documents (e.g., "PVA Tapioca Pearl Starch-Based Hydrogel + Curcumin" if both components are integral to the product). This will help avoid ambiguity and maintain alignment throughout the protocol.

2. **Title Issue**:
The title of the study does not mention curcumin, even though it is highlighted throughout the protocol as a key component of the intervention. To maintain consistency and accurately reflect the study's focus, the title should include curcumin.
3. **Operation Definition of Safety and Efficacy**:
The protocol does not provide clear definitions or criteria for measuring safety and efficacy. For example:
   - **Safety**: Specify the parameters to be used, such as the incidence of adverse events (AEs), serious adverse events (SAEs), or any specific clinical indicators of safety.
   - **Efficacy**: Define what constitutes successful wound healing (e.g., time to complete re-epithelialization, reduction in erythema, or pain relief).
4. **Sample Size Calculation**:
The protocol lacks critical information, such as the effect size estimate, which is essential for accurately calculating the required sample size. Effect size can typically be derived from pilot studies, previous related research, or expert opinion. Without this, the validity of the sample size calculation is questionable. Additionally, details about the assumptions used (e.g., variance, expected difference between groups) are missing. Include a reference article or supporting data to justify the effect size and other assumptions used in the sample size calculation.
5. **Data Analysis**:
The statistical analysis plan is incomplete. Key details are missing regarding how variables will be measured and analyzed. Specify the statistical methods to be used in more detail, including how outcomes like wound healing, erythema, and pain scores will be presented and analyzed. Add a plan for handling missing data to improve the results. Also explain details of independent and dependent variables for logistic regression analysis. Also, add details for single regression analysis.
6. Studies reporting the efficacy in burn wounds need to be presented for supporting the case.
7. Dose/ amount of curcumin contained in the dosage form is not specified
8. More information is required regarding form in which curcumin will be used in the dosage form (purified extract or otherwise)
9. Further clarification is required regarding the outcomes of the study, whether being safety/ efficacy of the drug or wound healing.
10. While the comparison between a standard and the treatment is made, base used is different in both of the preparations. Clarification is sought in this regard.
11. More explanation regarding the effects of curcumin after incorporation into the sheet along with hydrogel is required.
12. The IMP needs to be manufactured in GMP compliant facility, clarification is required.

08. The case was placed before the Committee for consideration. In order to avoid conflict of interest, the Secretary, CSC (being evaluator of the case) did not participated in voting. The Committee decided the case as under:

Decision: The CSC after deliberation decided to defer the case for fulfilment of the shortcomings and queries observed during the meeting.

09. Accordingly, the CSC Decision was communicated on 04th February 2025 and another shortcoming letter was also shared, yet response is awaited.

10. The case was placed before the CSC in its 55th meeting held on 28th February 2025. The Committee decided the case as follow:

Decision: The CSC after deliberation decided to defer the case for fulfilment of shortcomings communicated on vide letter 04th February, 2025.

The PI vide letter reference No. nil dated 21st March, 2025 responded to the shortcomings/ observations which were communicated by this office vide letter F. No. 16-54/2024 CSC on 04/02/2025. The response is presented below: -

(In order to avoid conflict of interest, the Secretary, CSC (being evaluator of the case) will not participate in voting.)

CSC's Comment-1: Clarification is sought whether IMP in the said study is "PVA Tapioca Pearl Starch-Based Hydrogel", "Curcumin", or a combination of both.
PI Response: The key focus of this study is the PVA-tapioca pearl starch-based hydrogel, which serves as an innovative wound-healing matrix. While curcumin is included as an active pharmaceutical ingredient (API), it is already extensively studied and widely recognized for its anti-inflammatory, antioxidant, and wound-healing properties. Given its well-documented efficacy and safety, curcumin is not the novel aspect of this research. Instead, the primary objective is to evaluate the hydrogel itself as a therapeutic intervention, including its role as a delivery matrix for curcumin.
CSC's Comment-2: The title of the study does not mention "Curcumin", Justification is required.
PI Response: The title in its current form accurately represents the primary objective of the study—assessing the PVA-tapioca pearl starch-based hydrogel for burn wound healing. While curcumin is not explicitly mentioned, the term "PVA-tapioca pearl starch-based hydrogel" effectively encompasses the full formulation, as the study aims to evaluate both the hydrogel's therapeutic potential and its role as a delivery matrix for curcumin. Additionally, curcumin's inclusion and significance are thoroughly detailed within the study protocol, ensuring clarity and transparency. Given this, we believe the title appropriately conveys the scope of the investigation with conciseness and relevance, without omitting any critical aspect of the investigation.
CSC's Comment-3: The study protocol does not provide clear definitions or criteria for measuring safety and efficacy.
PI Response: The study protocol defines efficacy primarily through the healing rate, assessed using photographic image analysis by an independent blinded evaluator. Complete wound epithelization will be the primary indicator of efficacy, ensuring an objective and standardized assessment. For safety, adverse events (AE) and serious adverse events (SAE) will be systematically recorded using standardized adverse event reporting forms. The incidence of AEs/SAEs and any changes in the management plan will be analyzed using stratified analysis and Chi-square tests, providing a robust approach to evaluating safety. Additionally, secondary endpoints such as erythema (graded on a predefined ordinal scale by an experienced radiotherapist) and pain scores (measured using a 10-point Visual Analog Scale, VAS) further support the assessment of both safety and efficacy. These methods are widely accepted in clinical trials and ensure a comprehensive evaluation of treatment outcomes. The protocol follows standard clinical trial practices in defining safety and efficacy, using objective and widely recognized assessment criteria.
CSC's Comment-4: Justification of the sample size is required.
PI Response: The sample size determination was based on statistical power calculations to ensure that the study has adequate sensitivity to detect meaningful differences between intervention and control groups. The calculations were made with: Significance level (α) = 0.05 (5% probability of Type I error) Power ($1-\beta$) = 0.8 (80% probability of detecting a true effect) Beta (β) = 0.2 (20% probability of Type II error) **For Phase-1,** a sample size of 16 patients per arm (total 32 patients) was required. To accommodate an expected

10% dropout rate, the total sample size was rounded to 36 patients (18 per group).

For Phase-2, a sample size of 22 patients per arm (total 44 patients) was required. With a 10% dropout rate, the final sample size was rounded to 50 patients (25 per group).
The chosen parameters for sample size calculation ($\alpha = 0.05$, $\beta = 0.2$, power = 80%) are widely accepted in clinical research, ensuring sufficient statistical power. These calculations ensure that the study has sufficient statistical power to evaluate the primary endpoints, including wound healing, erythema, and pain scores, without inflating the risk of false-negative or false-positive results.

CSC's Comment-5:
The statistical methods to be used for presentation and analysis of outcomes such as wound healing, erythema, and pain scores need to be explained clearly.

PI Response:
The study employs SPSS version 26.0 for statistical analysis, with the following methods applied to different outcome measures:

Primary Outcome:
Wound Healing rate will be determined using photographic image analysis, with evaluations by an independent blinded physician. Logistic regression will be used to determine the incidence of wound healing. Results will be reported as odds ratios (OR) with 95% confidence intervals (CI) to estimate the likelihood of complete wound epithelization in the intervention vs. control group.

Secondary Outcomes:
Erythema Assessment or Visual assessment by an experienced radiotherapist using an ordinal grading scale (0–9). As an ordinal variable, erythema will be analyzed using ordinal logistic regression to assess treatment effects. Data may also be presented as mean ± standard deviation or median (IQR) depending on distribution.
Pain Score Assessment will be measured using the Visual Analog Scale (VAS, 1–10). Pain scores (continuous variable) will be analyzed using an independent t-test (for normally distributed data) or Mann-Whitney U test (for non-normally distributed data). Mean pain scores will be presented as mean ± standard deviation (SD) or median (IQR).
Safety Outcomes: Adverse Events (AE/SAE)
Incidence of adverse events will be recorded using standardized forms. Chi-square test will be used to compare the frequency of AE/SAE between groups. Stratified analysis will assess how different patient subgroups are affected.
Simple regression analysis will be performed to adjust for potential confounders, ensuring unbiased treatment effect estimates.
This approach ensures rigorous statistical evaluation, appropriate handling of different data types, and clear reporting of study results. the statistical tests selected for analyzing wound healing, erythema, and pain scores align with established methodologies in similar dermatology trials.

CSC's Comment-6:
Studies reporting the efficacy of proposed intervention in burn wounds need to be presented.

PI Response:
Regarding studies on the efficacy of the proposed intervention in burn wounds, we would like to provide the following clarification:
We have conducted and presented detailed studies on the PVA-tapioca pearl starch-based hydrogel, demonstrating its biocompatibility, structural integrity, and suitability as a wound-healing matrix. The published results supporting its potential application can be retrieved at ***[Khalid, M., Jameel, F., Jabri, T., Jabbar, A., Salim, A., Khan, I., & Shah, M. R. (2024). α-Terpineol loaded, electron beam crosslinked polyvinyl alcohol/tapioca starch hydrogel sheets; fabrication, characterization and evaluation of wound healing potential on a full thickness acid burn wound. RSC advances, 14(38), 28058-28076. (Annexure 1)***
Furthermore, curcumin's role in burn wound healing has been extensively documented in the scientific literature, with numerous studies highlighting its anti-inflammatory, antioxidant, and antimicrobial properties, which are essential for tissue regeneration and wound repair. A number of these studies have been cited in the protocol.
While specific studies on the combination of this hydrogel with curcumin have not yet been conducted, the available experimental evidence on the matrix and the well-established therapeutic potential of curcumin provide a strong scientific basis for this investigation. Given the extensive prior research on both components, this study represents a logical and evidence-based progression.

CSC's Comment-7: Dose/amount of curcumin contained in the dosage form needs to be specified.
PI Response: The hydrogel formulation in this proposed clinical trial contains 1% curcumin by weight, relative to the volume of the polymeric solution used for hydrogel preparation. This concentration was selected based on literature reports demonstrating curcumin's wound-healing efficacy while maintaining biocompatibility and stability within the hydrogel matrix.
CSC's Comment-8: More information is required regarding the form in which curcumin will be used in the dosage form (purified extract or otherwise)
PI Response: Curcumin used in the formulation is in the form of a purified extract dried to a powder. It is incorporated into the hydrogel as a finely dispersed powder to ensure uniform distribution within the polymeric matrix.
CSC's Comment-9: Further clarification is required regarding the outcomes of the study, whether being safety /efficacy of the drug or wound healing.
PI Response: The proposed clinical trial aims to evaluate both the safety and efficacy of the investigational medicinal products (IMPs). The study will assess: **Safety** – Monitoring for any adverse effects related to the hydrogel formulation and curcumin incorporation. **Efficacy** – Evaluating the wound-healing potential of the hydrogel, including clinical improvement in burn wounds, healing rates, and overall treatment outcomes. By assessing both aspects, the study aims to provide comprehensive data on the hydrogel's therapeutic potential as a wound-healing matrix.
CSC's Comment-10: While the comparison between a standard and the treatment is made, the base used is different in both of the preparations, justifications is required.
PI Response: The choice of comparator/standard in this proposed clinical trial is based on the available standard treatments in the country. Currently, there are no marketed PVA-tapioca or curcumin-based hydrogels for direct comparison. Therefore, the selected standard treatment serves as a clinically relevant benchmark to assess the hydrogel's efficacy and safety in burn wound healing. This approach ensures that the study outcomes remain meaningful in the context of existing therapeutic options.
CSC's Comment-11: More explanation regarding the effects of curcumin after incorporation into the sheet along with hydrogel is required.
PI Response: The incorporation of curcumin into the PVA-tapioca pearl starch-based hydrogel sheet is expected to provide a combinatorial therapeutic effect, enhancing the overall wound-healing potential. Both the hydrogel matrix and curcumin exhibit anti-inflammatory properties, contributing to a synergistic effect in reducing inflammation, promoting tissue regeneration, and accelerating wound closure. Hydrogel Matrix Contribution: The PVA-tapioca hydrogel acts as a biocompatible scaffold, maintaining a moist wound environment, facilitating oxygen exchange, and supporting cellular migration and proliferation—key factors in efficient wound healing. Curcumin's Role: Curcumin, known for its antioxidant, antimicrobial, and anti-inflammatory properties, enhances the therapeutic potential of the hydrogel by reducing oxidative stress, modulating inflammatory pathways, and supporting angiogenesis. Expected Combined Effect: The integration of curcumin into the hydrogel sheet is anticipated to result in enhanced wound healing compared to conventional treatments by delivering curcumin in a sustained manner, increasing local bioavailability, and amplifying anti-inflammatory and regenerative effects. This combined approach aims to maximize wound-healing efficacy, providing an effective therapeutic option for burn injuries

CSC's Comment-12:
The IMP needs to be manufactured in GMP compliant facility; clarification is required.
PI Response:
IMP for this proposed clinical trial is being manufactured at Plot No. E-65, North Western Industrial Zone, Port Qasim, Karachi, which is GMP-compliant. The DRAP certification confirming GMP compliance was included in the original protocol submission. *(See Annexure 2)*

11. The case was placed before the CSC for consideration.

Decision: The CSC after consideration decided to defer the case for further deliberations.

12. The case was placed before the CSC for consideration.

Proceedings:

Prof. Dr. Raza Shah (Ph.D. Organic Chemistry), Director, ICCBS, University of Karachi, Karachi, joined the meeting through Zoom link and explained the trial design, technical aspects of the study. The CSC members raised many queries regarding Drug Delivery System and need/importance of the trial, manufacturing process of the IP.

13. The Committee decided the case as under:

Decision:

The CSC, after deliberation, decided to reject the Clinical Trial titled, "An Open-Label, Randomized, Positive-Controlled, Phase-I/II Clinical Trial to Evaluate the Safety and Efficacy of PVA Tapioca Pearl Starch-Based Hydrogel in Enhancing the Healing of Burn Wounds", due to the following reasons:

i. **None of the proposed sites (s) are licensed to act as Clinical Trial Sites for Phase-I/II Clinical Trials**
ii. **M/s Pak Electron Beam Irradiation (Pvt.) Ltd., Karachi, holding establishment licence (ELM-0033) is the proposed manufacturer for IMPs. Whereas, approval of the MDB/Concerned Authority for production of IMP has not be provided.**
iii. **The response of the PI to the queries of the CSC, communicated vide letter bearing F. No. 16-54/2024-CSC, dated 04/02/2025 was not found satisfactory by the Committee.**
iv. **The applicant is not qualifying the criteria as prescribed in the "Guidelines for Conduct of Clinical Research in Pakistan" made under the Bio-Study, 2017.**

CASE No. 3.6:

APPROVAL OF CLINICAL TRIAL TITLED "ABILITY OF THE VE818 TO REDUCE ENTEROPATHOGEN COLONIZATION AND IMPROVE ENVIRONMENTAL ENTEROPATHY IN PREGNANT WOMEN: A PROOF OF CONCEPT AND PHASE II RANDOMIZED, PLACEBO-CONTROLLED TRIAL IN BANGLADESH, PAKISTAN, ZAMBIA AND BURKINA FASO" AND IMPORT PERMISSION FOR VE818, VANCOMYCIN, PLACEBO AND FECAL SAMPLE COLLECTION DEVICE (CAPSCAN). F. No. 03-62/2024-CT (PS)

Dr. Syed Asad Ali, Professor of Community Health Sciences and Pediatrics and Chair Department of Community Health Sciences, Associate Dean Research, MC, Pakistan, The Noordin Noormahomed Sheriff Endowed Chair, Professor of Pediatrics and Community Health Sciences has requested for approval of subject cited Clinical Trial. Application was made on prescribed Form-I (printed on hospital letter head), along with a fee of Rs. 200,000/- deposited vide Slip number. 75644084761, dated 20th Feb, 2024.

2. Reference to pre-paras regarding request for approval/registration of Clinical Trial, application was assessed by the than Deputy Director (CTS-I) under the Bio Study Rules, 2017. deficiencies were conveyed to PI vide letter No. F. 03-56/2024-DD-PS dated 01-07-2024.

3. Following were the queries or information/documents required:

Sr. No.	DRAP Queries
1	Provide following data related to VE-818. a. Authentic pre-clinical studies and data of Phase-I trial b. Toxicity studies (including reproductive toxicology), Genotoxicity studies, Carcinogenicity studies, Mutagenic studies, Teratogenic studies and other Pharmacokinetic data including dosage selection. c. Antigenicity and immunogenicity studies.
2	Provide Safety and Performance studies of CapScan Medical Device in pregnant women.
3	Provide Safety studies of Vancomycin in pregnant women.
4	Provide clarification on protocol design for the use of antibiotic (Vancomycin) in healthy pregnant women in the absence of any infectious disease as it will promote Antimicrobial Resistance (AMR).
5	As per submitted documents, proposed clinical trial steps like screening, ICF, administration of LPs and collection of samples (pre and post administration) will be conducted at antenatal clinics / homes from different union councils of Matiari District. As per Bio-Study Rules 2017, Trial procedures can be done only at licensed clinical trial site(s).
6	Provide details of Gynecology & Obstetrics doctors in the Research team as Clinical Trial is to be conducted on Pregnant women.
7	a. Provide composition (names and designations) of IRB. b. In IRB approval dated 21" January 2024, many names have been mentioned without any relevance to study.
8	Provide summary of Protocol.
9	Provide summary of Investigator's Brochure.
10	Provide Names of Monitors and Clinical Research Associate.
11	a. Provide GMP Certificates for following companies duly issued by regulatory authority. i. Manufacturer of Vancomycin. ii. Manufacturer of VE818 iii. Manufacturer of Placebo b. Provide ISO Certificates for following companies. i. Manufacturer of CapScan ii. Manufacturer of Stool collection tube iii. Manufacturer of Saliva collection kit
12	Provide CoPP (Certificate of Pharmaceutical Product) or Free Sale Certificate or regulatory status for following products, duly issued by regulatory authority. i. Vancomycin. ii. VE818 iii. iCapScan iv. Placebo v. Stool collection tube vi. Saliva collection kit
13	Provide label of Investigational Product.
14	Provide authorization of sponsor to the principal investigator/institution for the conduct of clinical trial.
15	Insurance Statement is not present in the Informed Consent Form (ICF). Therefore, provide insurance details (medical treatment cost in case of any SAE and compensation in case of any fatality) of subjects and submit informed Consent Form as per format of ICH GCP guidelines.
16	a. List of tests to be conducted outside Pakistan with justifications and SOP for the transportation for Biological samples. b. b. List of tests to conducted in Pakistan with details of testing laboratory.

4. In response to above mentioned letter No. F. 03-56/2024-DD-PS dated 01-07-2024 from DRAP, Dr. Syed Asad Ali, PI, AKUH, Karachi responded with following letters along with attachments:

i. Subject: Response to DRAP Queries on Assessment of Clinical Trial Application "ABILITY OF VE81B TO REDUCE ENTROPATHOGENS COLONIZATION AND IMPROVE ENVIRONMENTAL ENTEROPATHY IN PREGNANT WOMEN: A PROOF OF CONCEPT AND PHASE-II RANDOMIZED PLACEBO CONTROLLED TRIAL IN BANGLADESH, PAKISTAN, ZAMBIA, AND BURKINA FASO" dated 29th July 2024.

ii. Subject: Response to DRAP Queries on Assessment of Clinical Trial Application "ABILITY OF VE81B TO REDUCE ENTROPATHOGENS COLONIZATION AND IMPROVE ENVIRONMENTAL ENTEROPATHY IN PREGNANT WOMEN: A PROOF OF CONCEPT AND PHASE-II RANDOMIZED PLACEBO CONTROLLED TRIAL IN BANGLADESH, PAKISTAN, ZAMBIA, AND BURKINA FASO" dated 16th August 2024.

iii. Subject: Response to DRAP Queries on Assessment of Clinical Trial Application "ABILITY OF VE81B TO REDUCE ENTROPATHOGENS COLONIZATION AND IMPROVE ENVIRONMENTAL ENTEROPATHY IN PREGNANT WOMEN: A PROOF OF CONCEPT AND PHASE-II RANDOMIZED PLACEBO CONTROLLED TRIAL IN BANGLADESH, PAKISTAN, ZAMBIA, AND BURKINA FASO" dated 23rd August 2024.

5. Applicant has responded above letters as follows:

Subject: Response to DRAP Queries on Assessment of Clinical Trial Application "ABILITY OF VE81B TO REDUCE ENTROPATHOGENS COLONIZATION AND IMPROVE ENVIRONMENTAL ENTEROPATHY IN PREGNANT WOMEN: A PROOF OF CONCEPT AND PHASE-II RANDOMIZED PLACEBO CONTROLLED TRIAL IN BANGLADESH, PAKISTAN, ZAMBIA, AND BURKINA FASO" dated 29th July 2024.

Sr.	DRAP Comments	Response
1	Provide the following data related to VE-818. A. Authentic pre-clinical studies and data of Phase-I trial B. Toxicity studies (including reproductive toxicology), Genotoxicity studies, Carcinogenicity studies, Mutagenic studies, Teratogenic studies and other Pharmacokinetic data including dosage selection C. Antigenicity and immunogenicity studies.	**Pre-clinical Studies:** VE818 has been shown reduce inflammation in pre-clinical models of colitis via the production of immunomodulating metabolites and regulatory T cells and displacement of Grant-negative pathogens known to cause inflammation. Efficacy and strain characterization studies demonstrated the lack overt toxicity in mice as well as the absence of virulence factors and clinically relevant antibiotic resistance genes. (refer to IB page 10-11) **Phase-I Trial:** VE818 was administered to 52 subjects, with 22 receiving a placebo. It was well tolerated with no severe adverse events (SAEs) related to the drug. Common adverse events (AEs) reported were headache oropharyngeal discomfort, abdominal pain, abnormal gastrointestinal sounds, and nasopharyngitis. Severe AEs included apathy and deafness, which were likely unrelated to VE818. Phase 1 trial results file have been attached. Please note VE818 was previously known as JNJ-67670187. **Toxicity Studies:** Due to the commensal nature of the bacteria comprising VE818 and the lack of appropriate animal models that can mimic the interactions between the microbiome and its host, traditional toxicology studies were not conducted and have not been requested by any regulatory agency for Vedanta's live bio-therapeutic products (LBPs). Characterization of each individual bacterial strain in the LBP is required to build a product safety profile. This includes antibiotic-susceptibility, presence of virulence and antibiotic-resistance genes (ARG) and assessing the risk of genetic mobility. This approach is supported by regulatory agency interactions in the setting of other investigational LBPs from Vedanta. All 11 bacteria in VE818 have not been associated with infection, were resistant to multiple antibiotics from various antibiotic classes and did not contain virulence factors or clinically relevant ARGs in their genomes. Taken together, this evidence points towards a favorable safety profile. Importantly, VE818 showed no overt toxicity in mice, and it was shown to be safe and well-tolerated in healthy adults. **Reproductive Toxicology:** There are no appropriate animal models for reproductive toxicology evaluation in the context of LBPs.

		Therefore, safety in pregnancy was assessed by evaluating the prevalence and abundance of VE818-related species in pregnant women across various geographies including Pakistan. This analysis showed that VE818 species are common members of the microbiome of healthy pregnant women and therefore, carry minimal risk. Supporting this, data from the AMANHI study conducted in pregnant women from Pakistan showed that VEB18-species were correlated with positive pregnancy outcomes (study attached). **Genotoxicity:** Genotoxicity studies have not been conducted and have not been requested for any regulatory agency for Vedanta's LBPs. Bacteria do not have the same distribution properties as small molecules and therefore are not expected to interact with DNA. **Carcinogenicity, Mutagenic, and Teratogenic Studies:** No carcinogenicity, mutagenic and teratogenic studies have been conducted and have not been requested for any regulatory agency for Vedanta's LBPs. The organisms in VEB18 represent commensal bacteria residing within a healthy human intestinal microbiota and do not have known carcinogenic, mutagenic or teratogenic potential. **Pharmacokinetic Data and Dosage Selection:** Classical pharmacokinetic studies are not applicable to this type of product. However, in healthy-volunteers 14-daily doses of VE818 after vancomycin pretreatment was the most optimal dose leading to VE818 intestinal colonization for several weeks, which is key for efficacy. A short course of Vancomycin before VE818 was required for abundant and durable colonization, even at high doses (RTR-0027). In this Phase 1 study, VE818 was well tolerated with few side effects, mainly gastrointestinal symptoms. **Antigenicity and immunogenicity Studies:** The safety profile of VE818 indicates minimal risk of antigenicity. The strains in VE818 are normal commensal organisms found in the human GI tract and have been shown to be prevalent and abundant within the internal microbiome. In the intestine, they have been demonstrated to stimulate a population of FoxP3+CD4+ Treg cells in the colonic mucosa and augment the production of secondary bile acids. These Treg cells and metabolites are associated with the clinical effect of reducing colonic inflammation in mouse models of colitis.
2	Provide Safety and Performance studies of CapScan Medical Device in pregnant women.	The CapScan device to be used in this study was successfully implemented in EMP Trial I in Pakistan (AKU ERC number 2022-6889 -22802), Bangladesh (icddr, b ERC number PR-22084) and Zambia (TROPGAN ZAMRA Number: DMS/7/9/22/CT128). The 90 participants of these studies were also women in their second trimester of pregnancy and no adverse events were observed. It was well accepted by participants.
3	Provide Safety studies of Vancomycin in pregnant women.	Oral vancomycin is classified as a Pregnancy Category B drug by the FDA. This classification indicates that animal reproduction studies have not shown a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. It is poorly absorbed from the gastrointestinal tract, leading to minimal systemic absorption. This suggests a lower risk of fetal exposure compared to the intravenous formulation. A study by Goyal et al. found that the pharmacokinetics of oral vancomycin in pregnant women were consistent with non-pregnant adults, indicating that dosing regimens used for non-pregnant patients may also be applicable to pregnant patients (Goval et at 2022). Oral vancomycin is generally considered to be safe in pregnancy and lactation (ref) and it is routinely used during pregnancy to treat CDI without any safety concerns (Weiss et al 2012).
4	Provide clarification on	Vancomycin has been used pretty routinely in academic and industry

	protocol design for the use of antibiotic (Vancomycin) in healthy pregnant women in the absence of any infectious disease as it will promote Antimicrobial resistance	studies for a decade or more as pretreatment before fecal microbiota transplantation (FMT) or live bio therapeutic product (LBP) administration. Oral vancomycin was chosen because it is a narrow spectrum antibiotic (activity against Gram-positive organisms only) and does not have systemic absorption or action. Due to the short duration of the treatment (i.e., 5 days), development of vancomycin resistance is highly unlikely and if it were to occur, it'd be mostly a concern among Enterococci and Staphylococci. Enterococci are a part of the human gut microbiome but are not prevalent in LMICs. Staphylococci are not intestinal dwellers and live predominantly on the skin. In populations where Enterococci are prevalent, vancomycin resistant Enterococcus (VRE) colonization is not associated with vancomycin treatment in ICU patients (Munck et al 2020) oi in patients being treated for C. difficile infection (Stevens et at 2019). Broad-spectrum antibiotics like azithromycin and cephalosporins carry a much higher risk for developing resistance because they target Gram negative pathogens (e.g. E. Coli, Klebsiella) which are highly prevalent in the microbiome of adults and children from LMICs and can develop resistance much more rapidly than Gram positives.
5	As per the submitted documents, proposed clinical trial steps like screening, ICF, administration of IPs and collection of samples (pre and post-administration) will be conducted at antenatal clinics/homes from different union councils of Matiari District. As per Bio-Study Rules 2017, Trial procedures can be done only at licensed clinical trial site(s).	Given that this is a field-based trial involving a daily supplement, collecting simple data such as survey responses within participants' homes is justifiable. The collection of simple biological samples at home is also reasonable due to the impracticality of regular site visits for participants. However, all complex study-related procedures, such as antenatal ultrasounds, will be conducted at the licensed clinical trial site, aligning with regulatory requirements.
6	Provide details of Gynecology & Obstetrics doctors in the Research team as Clinical Trial is to be conducted on Pregnant women.	Dr. Sana Zahiruddin (FCPS) is a consultant gynecologist and is co-investigator of this trial. She will be looking after all our referral cases and will provide necessary treatment. Dr. Ghulam Sugra who will i.re responsible for enrollment at Matiari site has 20 years of experience in gynecology. Dr. Waheeda has implemented maternal studies in Matiari and has experience of more than 15 years. Dr. Jabeen has more than 12 years of experience in Matiari and has implemented AMANHI and PP sepsis projects. Their CVs are attached to this submission.
7	a. Provide composition (names and designations) of IRB. b. In IRB approval dated 21-Jan-2024, many names have been mentioned without any relevance to study.	We are sharing the updated ERC committee members list. Members are selected based on their specialty. From the list, it is obvious that it covers areas from gynecology/obstetrics, pharmacy, radiology and pediatrics. This trial has relevance to all these specialties.
8	Provide summary of Protocol	Summary of protocol is in Annexure 1 We are submitting it with this response.
9	Provide summary of investigator's Brochure.	Summary OF VE818, CapScan and Vancomycin updated in annexure 10.
10	Provide Names of Monitors and Clinical Research Associate	FHI Clinical had been selected by BMGF as a monitor for this trial. A detailed description of CRO and its proposed monitoring visits are shared in a letter.
	a. Provide GMP Certificates for following companies duly issued by regulatory authority.	We have attached following documents: 1. GMP certification from ANI Pharmaceuticals (manufacturer of vancomycin).

	Manufacturer of Vancomycin. Manufacturer of VE818 Manufacturer of Placebo b. Provide ISO Certificates for following companies Manufacturer of CapScan Manufacturer of Stool collection tube Manufacturer of Saliva collection kit	2.The original FDA registration approval letter (Reg. # 050606) from the FDA/HHS for the Vancomycin – this serves as proof of regulatory status 3. A memo from ANI's regulatory affairs director setting out their proof of ownership of the product originally registered as well as the registration of the product with the FDA. 4. The Standard Pharmaceutical Product Description. It links the details up to the FDA registration number. GMP of VE818 and placebo manufacturer Vedanta is attached. **CapScan:** manufacturer's ISO 13485:2016 certification attached **Stool collection:** Sarstedt 2 ml screw cap tube, sterile (cat. no. 72.694.306). Manufacturer's ISO 13485:2016 certification and product Declaration of Conformity attached. **Saliva kit** manufacturing facility ISO 13485:2016 certification is attached.
11	Provide CoPP (Certificate of Pharmaceutical Product) or Free Sale Certificate or regulatory status for following products duly issued by regulatory authority: i. Vancomycin ii. VE818 iii. CapScan iv. Placebo v. Stool Collection tube vi. Saliva collection kit	The manufacturer of Vancomycin, ANI pharmaceuticals has applied for a CoPP from the FDA to further satisfy the requirements for Pakistan. This apparently can take 10-20 days to receive from the FDA. Vedanta Biosciences Inc. a biotechnology company manufactures the VE818 clinical stage drug substance and product at two Massachusetts sites. The company adheres to current Good Manufacturing Practices (CGMP) as specified by U.S. and international guidelines, though it has not yet been inspected by the FDA. Each batch undergoes rigorous testing, and a Certificate of Analysis is issued for all drug substances and products. Detailed statement of justification by the Vedanta company is attached. The CapScan devices are used only in clinical research studies approved by the respective institution's Ethics Committees (IRB. ERC). The devices are considered by the approving IRBs as non-significant risk devices and therefore do not require IDE approval in the USA. Furthermore, exporting the non-significant risk device for research clinical study can be considered permissible under FDA sections 801(e)(1). Justification is provided in annexure 13b and NSR statement by CapScan is also attached. EU Declarations of Conformity for the saliva collection kit and stool collection tube attached.
12	Provide label of investigational Product	Label files are attached
13	Provide authorization of sponsor to the principal investigator/institution for the conduct of clinical trial.	Authorization letter is attached
14	The insurance Statement is not present in the Informed Consent Form (ICF). Therefore, provide insurance details (medical treatment cost in case of any SAE and compensation in case of any fatality) of subjects and submit informed Consent Form as per format of ICH GCP guidelines	All of our trial participants are covered under insurance (insurance email attached) Compensation details are provided in protocol **section 23.0** (page 50) and in trial consent is covered in **possible risks and discomfort heading** (page 6)
15	a. List of tests to be conducted	

	outside Pakistan with justifications and SOP for the transportation for Biological samples. b. List of tests to be conducted in Pakistan with details of testing laboratory.	<table><tr><th>List of tests to be performed outside Pakistan</th><th>List of tests to be performed inside Pakistan</th></tr><tr><td>Lactulose/rhamnose (L/R) Assay</td><td>ELISA Assays</td></tr><tr><td>Metabolomics</td><td>Metagenomics</td></tr><tr><td>Metatranscriptomics</td><td>TaqMan Array Card Assays</td></tr><tr><td>Proteomics</td><td></td></tr></table>Sample shipment SOP is shared. Justifications of tests outside Pakistan is the lack of assay/facility/testing within the country. Details of testing laboratory within Pakistan is IDRL in Karachi AKU. Further information is mentioned in protocol on page 37.

Subject: Response to DRAP Queries on Assessment of Clinical Trial Application "ABILITY OF VE81B TO REDUCE ENTROPATHOGENS COLONIZATION AND IMPROVE ENVIRONMENTAL ENTEROPATHY IN PREGNANT WOMEN: A PROOF OF CONCEPT AND PHASE-II RANDOMIZED PLACEBO CONTROLLED TRIAL IN BANGLADESH, PAKISTAN, ZAMBIA, AND BURKINA FASO" dated 16th August 2024.

Sr.	DRAP Comments	Response
1	Provide the following data related to VE-818. A. Authentic pre-clinical studies and data of Phase-I trial B. Toxicity studies (including reproductive toxicology), Genotoxicity studies, Carcinogenicity studies, Mutagenic studies, Teratogenic studies and other Pharmacokinetic data including dosage selection C. Antigenicity and immunogenicity studies.	Probiotic administration is generally safe and well tolerated by pregnant women with minimal risk to the developing fetus. In the first clinical trial of the Experimental Medicine Platform (EMP), we used the well-characterized probiotic Vivomixx. No serious adverse events were observed that could be attributed to the intervention. In this second trial in the EMP series, we will be testing VE818, which is composed of bacterial strains that are naturally occurring commensals found in the GI tract. VE818 is a probiotic categorized as a live bio-therapeutic product. VES18 is designed to displace pathogenic bacteria while promoting the growth of beneficial microbes, which are already present in the GI tract of pregnant women. All bacterial species in VE818 are members of the Clostridia class and are strict obligate anaerobes, meaning they cannot survive outside the intestine due to the presence of oxygen. In the rare event of translocation into the bloodstream and infection, multiple antibiotics of different classes have been identified that could be used to target each of the VE818 strains. Phase 1 clinical trial results are promising, demonstrating effective colonization of VE818 strains with minimal adverse events, indicating its potential as a safe and beneficial therapeutic option. Furthermore, a composition similar to VE818 has been shown to be safe and efficacious at reducing *Clostridiodes difficile* recurrence in patients suffering from *C. difficile* infection (CDI). (https://pubmed.ncbi.nlm.nih.gov/37060545/) Detailed response Pre-Clinical Studies: VE818 has been shown to reduce inflammation in pre-clinical models of colitis via the production of immunomodulating metabolites and regulatory T cells and displacement of Gram-negative pathogens known to cause inflammation. Efficacy and strain characterization studies demonstrated the lack overt toxicity in mice as well as the absence of virulence factors and clinically relevant antibiotic resistance genes (refer to IB page 10-11). **Detailed response Pre-Clinical Studies:** VE818 has been shown reduce inflammation in pre-clinical models of colitis via the production of immunomodulating metabolites and regulatory T cells and displacement of Grant-negative pathogens known to cause inflammation. Efficacy and strain characterization studies demonstrated the lack overt toxicity in mice as well as

		the absence of virulence factors and clinically relevant antibiotic resistance genes. (refer to IB page 10-11) **Phase-I Trial:** VE818 was administered to 52 subjects, with 22 receiving a placebo. It was well tolerated with no severe adverse events (SAEs) related to the drug. Common adverse events (AEs) reported were headache oropharyngeal discomfort, abdominal pain, abnormal gastrointestinal sounds, and nasopharyngitis. Severe AEs included apathy and deafness, which were likely unrelated to VE818. Phase 1 trial results file have been attached. Please note VE818 was previously known as JNJ-67670187. **Toxicity Studies:** Due to the commensal nature of the bacteria comprising VE818 and the lack of appropriate animal models that can mimic the interactions between the microbiome and its host, traditional toxicology studies were not conducted and have not been requested by any regulatory agency for Vedanta's live bio-therapeutic products (LBPs). Characterization of each individual bacterial strain in the LBP is required to build a product safety profile. This includes antibiotic-susceptibility, presence of virulence and antibiotic-resistance genes (ARG) and assessing the risk of genetic mobility. This approach is supported by regulatory agency interactions in the setting of other investigational LBPs from Vedanta. All 11 bacteria in VE818 have not been associated with infection, were resistant to multiple antibiotics from various antibiotic classes and did not contain virulence factors or clinically relevant ARGs in their genomes. Taken together, this evidence points towards a favorable safety profile. Importantly, VE818 showed no overt toxicity in mice, and it was shown to be safe and well-tolerated in healthy adults. **Reproductive Toxicology:** There are no appropriate animal models for reproductive toxicology evaluation in the context of LBPs. Therefore, safety in pregnancy was assessed by evaluating the prevalence and abundance of VE818-related species in pregnant women across various geographies including Pakistan. This analysis showed that VE818 species are common members of the microbiome of healthy pregnant women and therefore, carry minimal risk. Supporting this, data from the AMANHI study conducted in pregnant women from Pakistan showed that VEB18-species were correlated with positive pregnancy outcomes (study attached). **Genotoxicity:** Genotoxicity studies have not been conducted and have not been requested for any regulatory agency for Vedanta's LBPs. Bacteria do not have the same distribution properties as small molecules and therefore are not expected to interact with DNA. **Carcinogenicity, Mutagenic, and Teratogenic Studies:** No carcinogenicity, mutagenic and teratogenic studies have been conducted and have not been requested for any regulatory agency for Vedanta's LBPs. The organisms in VEB18 represent commensal bacteria residing within a healthy human intestinal microbiota and do not have known carcinogenic, mutagenic or teratogenic potential. **Pharmacokinetic Data and Dosage Selection:** Classical pharmacokinetic studies are not applicable to this type of product. However, in healthy-volunteers 14-daily doses of VE818 after vancomycin pretreatment was the most optimal dose leading to VE818 intestinal colonization for several weeks, which is key for efficacy. A short course of Vancomycin before VE818 was required for abundant and durable colonization, even at high doses (RTR-0027). In this Phase 1 study, VE818 was well tolerated with few side effects, mainly gastrointestinal symptoms. **Antigenicity and immunogenicity Studies:** The safety profile of VE818

		indicates minimal risk of antigenicity. The strains in VE818 are normal commensal organisms found in the human GI tract and have been shown to be prevalent and abundant within the internal microbiome. In the intestine, they have been demonstrated to stimulate a population of FoxP3+CD4+ Treg cells in the colonic mucosa and augment the production of secondary bile acids. These Treg cells and metabolites are associated with the clinical effect of reducing colonic inflammation in mouse models of colitis. Because of the safe profile of this product which basically includes healthy bacteria that are already present in the GI tract of women worldwide, this trial has already received regulatory approval from the regulatory body in Bangladesh.
2	Provide Safety and Performance studies of CapScan Medical Device in pregnant women.	we are using the same device for this trial which was approved by DRAP for EMP trial 1 (F.No.16-39/2023-CSC) CapScan is a non-invasive, single use intestinal sampling device that can profile human gut microbiome and metabolome under physiological conditions. The safety of the Capscan device was evaluated in a clinical study involving 15 healthy volunteers, with no adverse events reported. The WCG IRB deemed CapScan a non-significant risk device, eliminating the need for an FDA IDE. Subjects, aged 22 to 64, ingested a total of 290 CapScan devices, all of which were successfully recovered, confirming the device's benign safety profile. See published article here: (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10191855/) The CapScan device to be used in this study was successfully implemented in EMP Trial I in Pakistan (AKU ERC number 2022-6889 -22802), Bangladesh (icddr, b ERC number PR-22084) and Zambia (TROPGAN ZAMRA Number: DMS/7/9/22/CT128). A total of 90 pregnant women in their second trimester of pregnancy across 3 countries were administered 4 capsules each and no adverse events were observed. All capsules were retrieved from the stool. The device was well tolerated and well accepted by all the participants Although enrollment and follow-up through birth has been completed for EMP Trial I, the study is still ongoing as we are following up all participants and their infants up until 1 year of age. Therefore, these results have not been published yet.
3	Provide Safety studies of Vancomycin in pregnant women.	Oral vancomycin is classified as a Pregnancy Category B drug by the FDA. This classification indicates that animal reproduction studies have not shown a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. It is poorly absorbed from the gastrointestinal tract, leading to minimal systemic absorption. This suggests a lower risk of fetal exposure compared to the intravenous formulation. Below is the link to the FDA Orange Book for Vancomycin hydrochloride capsules. Search for Vancomycin product code 50606. https://www.accessdata.fda. gov/scripts/cder/ob/search_product.cfm Detailed label information can be found here httos://dailvmed.nlm.nih.sovldailvmed/eetFile.cfm?setid=a078d9c2-f89c-4f9f-8ded-60ffb2983c3f&tvpe=pdf Safety for pregnant women is mentioned on page 7.
4	Provide clarification on protocol design for the use of antibiotic (Vancomycin) in healthy pregnant women in the absence of any infectious disease as it will promote Antimicrobial resistance	Oral vancomycin was chosen because it is a narrow spectrum antibiotic (activity against Gram-positive organisms only) and does not have systemic absorption or action. Due to the short duration of the treatment (i.e., 5 days), development of vancomycin resistance is highly unlikely and if it were to occur, it'd be mostly a concern among Enterococci and Staphylococci. Enterococci are a part of the human gut microbiome but are not prevalent in LMICs. Staphylococci are not intestinal dwellers and live predominantly on the skin. In populations where Enterococci are prevalent, vancomycin resistant Enterococcus (VRE) colonization is not associated with vancomycin treatment

		in ICU patients (Munck et al 2020) oi in patients being treated for C. difficile infection (Stevens et at 2019). Broad-spectrum antibiotics like azithromycin and cephalosporins carry a much higher risk for developing resistance because they target Gram negative pathogens (e.g. E. Coli, Klebsiella) which are highly prevalent in the microbiome of adults and children from LMICs and can develop resistance much more rapidly than Gram positive bacteria. Several studies have shown that probiotic strain colonization is significantly enhanced by pretreatment with 5 days of oral vancomycin. (Shen 2015; Bobilev 2019; Dsouza 2022). In Vedanta's Phase 1 study (Figure 13 of IB), administration of VE818 with vancomycin pretreatment led to robust strain colonization. Among those subjects who did not receive vancomycin pretreatment, no strains were detected after 14 days of dosing with VE818. This benefit was also shown for VE303 (Dsouza 2022). Importantly, strain colonization of the intestine is required for efficacy. Oral vancomycin has a favorable safety profile compared to other antibiotics, including as treatment for CDI in pregnancy. It has been used routinely in academic and industry studies for a decade or more as pretreatment before fecal microbiota transplantation (FMT) or live bio therapeutic product (LBP) administration. Oral vancomycin is being administered under carefully controlled conditions with rigorous monitoring. The potential risks are mitigated by the short duration and low dose, alongside comprehensive screening and follow-up to monitor any adverse effects. The study design ensures that any risks are outweighed by the potential benefits of reducing enteropathogen colonization and improving maternal and neonatal health outcomes.
5	As per the submitted documents, proposed clinical trial steps like screening, ICF, administration of IPs and collection of samples (pre and post-administration) will be conducted at antenatal clinics/homes from different union councils of Matiari District. As per Bio study Rules 2017, trial procedures can be done only at licensed clinical trial site(s).	We have revised our protocol and informed consent, and ultrasound procedures will take place at the Matiari site. All stools collected from participants will be processed at the Matiari site.
6	Provide details of Gynecology & Obstetrics doctors in the Research team as Clinical Trial is to be conducted on Pregnant women.	Dr. Sana Zahiruddin (FCPS) is a consultant gynecologist and is co-investigator of this trial. She will be looking after all our referral cases and will provide necessary treatment. Dr. Ghulam Sugra who will i.re responsible for enrollment at Matiari site has 20 years of experience in gynecology. Dr. Waheeda has implemented maternal studies in Matiari and has experience of more than 15 years. Dr. Jabeen has more than 12 years of experience in Matiari and has implemented AMANHI and PP sepsis projects. Their CVs are attached to this submission.
7	a. Provide composition (names and designations) of IRB. b. In IRB approval dated 21-Jan-2024, many names have been mentioned without any relevance to	We are sharing the updated ERC committee members list. Members are selected based on their specialty. From the list, it is obvious that it covers areas from gynecology/obstetrics, pharmacy, radiology and pediatrics. This trial has relevance to all these specialties.

	study.	
8	Provide summary of Protocol	Summary of protocol is in Annexure 1 We are submitting it with this response.
9	Provide summary of investigator's Brochure.	Summary OF VE818, CapScan and Vancomycin updated in annexure 10.
10	Provide Names of Monitors and Clinical Research Associate	FHI Clinical had been selected by BMGF as a monitor for this trial. A detailed description of CRO and its proposed monitoring visits are shared in a letter.
11	a. Provide GMP Certificates for following companies duly issued by regulatory authority. Manufacturer of Vancomycin. Manufacturer of VE818 Manufacturer of Placebo b. Provide ISO Certificates for following companies Manufacturer of CapScan Manufacturer of Stool collection tube Manufacturer of Saliva collection kit	We have attached following documents: 1. GMP certification from ANI Pharmaceuticals (manufacturer of vancomycin). 2.The original FDA registration approval letter (Reg. # 050606) from the FDA/HHS for the Vancomycin – this serves as proof of regulatory status 3. A memo from ANI's regulatory affairs director setting out their proof of ownership of the product originally registered as well as the registration of the product with the FDA. 4. The Standard Pharmaceutical Product Description. It links the details up to the FDA registration number. Below is the link to the FDA Orange Book for Vancomycin hydrochloride capsules. Search for Vancomycin product code 50606. (https://www.accessdata.fda.gov/scripts/cder/ob/search_product.cfm) GMP certificate issued by Vedanta Biosciences, the manufacturer of VE818 and placebo, is attached, as well as the Statement of GMP compliance for one of the VE818 batches. As a clinical stage manufacture with no commercial product, Vedanta has not yet been inspected by the FDA. Vedanta Biosciences is a clinical stage microbiome company based in Massachusetts. Manufacturing of VE818 drug substance and drug product takes place at two Massachusetts sites. The company adheres to current Good Manufacturing Practices (CGMP) as specified by U.S. and international guidelines. Each batch undergoes rigorous testing, and a Certificate of Analysis is issued for all drug substances and products. Detailed statement of justification by Vedanta is attached. **CapScan:** manufacturer's ISO 13485:2016 certification attached **Stool collection:** Sarstedt 2 ml screw cap tube, sterile (cat. no. 72.694.306). Manufacturer's ISO 13485:2016 certification and product Declaration of Conformity attached. **Saliva kit** manufacturing facility ISO 13485:2016 certification is attached.
12	Provide CoPP (Certificate of Pharmaceutical Product) or Free Sale Certificate or regulatory status for following products duly issued by regulatory authority: i. Vancomycin ii. VE818 iii. CapScan iv. Placebo v. Stool Collection tube vi. Saliva collection kit	The manufacturer of Vancomycin, ANI pharmaceuticals has applied for a Certificate of Pharmaceutical Product from the FDA to further satisfy the requirements for Pakistan. ANI is expecting a response from the FDA on the CoPP the week of August 19th. Vedanta Biosciences is a clinical stage microbiome company based in Massachusetts. Manufacturing of VE818 drug substance and drug product takes place at two Massachusetts sites. The company adheres to current Good Manufacturing Practices (CGMP) as specified by U.S. and international guidelines. Each batch undergoes rigorous testing, and a Certificate of Analysis is issued for all drug substances and products. Detailed statement of justification by Vedanta is attached. The CapScan devices are used only in clinical research studies approved by the respective institution's Ethics Committees (IRB, ERC). The approving IRBs consider the devices as non-significant risk devices and therefore do not require IDE approval in the USA. Furthermore, exporting the non-significant risk device for research clinical study can be considered permissible under FDA sections 801(e)(1). Justification is provided in Annexure 13b and NSR statement

		by CapScan is also attached. EU Declarations of Conformity for the saliva collection kit and stool collection tubes are attached.
13	Provide label of investigation al Product	Label files are attached
14	Provide authorization of sponsor to the principal investigator/institution for the conduct of clinical trial.	Authorization letter is attached
15	The insurance Statement is not present in the Informed Consent Form (ICF). Therefore, provide insurance details (medical treatment cost in case of any SAE and compensation in case of any fatality) of subjects and submit informed Consent Form as per format of ICH GCP Guidelines	All of our trial participants are covered under insurance (insurance email attached). Compensation details are provided in protocol section 23.0 (page 50) and in trial consent is covered in possible risks and discomfort heading (page 6). We have now provided more details in the protocol.
16	a. List of tests to be conducted outside Pakistan with justifications and SOP for the transportation for Biological samples. b. List of tests to be conducted in Pakistan with details of testing laboratory.	<table><tr><th>List of tests to be performed outside Pakistan</th><th>List of tests to be performed inside Pakistan</th></tr><tr><td>Lactulose/rhamnose (L/R) Assay</td><td>ELISA Assays</td></tr><tr><td>Metabolomics</td><td>Metagenomics</td></tr><tr><td>Metatranscriptomics</td><td>TaqMan Array Card Assays</td></tr><tr><td>Proteomics</td><td></td></tr></table> Sample shipment SOP is shared. Justifications of tests outside Pakistan is the lack of assay/facility/testing within the country. Details of testing laboratory within Pakistan is IDRL in Karachi AKU. Further information is mentioned in protocol on page 37.

Subject: Response to DRAP Queries on Assessment of Clinical Trial Application "ABILITY OF VE81B TO REDUCE ENTROPATHOGENS COLONIZATION AND IMPROVE ENVIRONMENTAL ENTEROPATHY IN PREGNANT WOMEN: A PROOF OF CONCEPT AND PHASE-II RANDOMIZED PLACEBO CONTROLLED TRIAL IN BANGLADESH, PAKISTAN, ZAMBIA, AND BURKINA FASO" dated 23rd August 2024.

We appreciate your thorough review of our clinical trial application and the opportunity to provide additional information in response to point 12, we are attaching the CoPP of vancomycin.

6. Reference pre paras, remarks of evaluator are as follows:

Sr. No.	Evaluator Remarks
1	Following data related to VE-818 is provided: a. Authentic pre-clinical studies (provided) and data of Phase-I trial (JNJ-67670187) b. Toxicity studies (including reproductive toxicology (not conducted), Genotoxicity studies (not conducted), Carcinogenicity studies (not conducted), Mutagenic studies (not conducted), Teratogenic studies (not conducted) and other Pharmacokinetic data including dosage selection (not conducted). c. Antigenicity and immunogenicity studies (not conducted).

2	Safety and Performance studies of CapScan Medical Device in pregnant women: The device was used in EMP I trail which is approved by DRAP.
3	Safety studies of Vancomycin in pregnant women: Pregnancy B category drug
4	As per submitted documents, proposed clinical trial steps like screening, ICF, administration of LPs and collection of samples (pre and post administration) will be conducted at antenatal clinics / homes from different union councils of Matiari District. As per Bio-Study Rules 2017, Trial procedures can be done only at licensed clinical trial site(s). Furthermore, Matiari site (Matiari Research & Training Center, Matiari operated under AKU) is not approved for above mentioned Clinical Study (Phase-II).
5	Provided CVs evaluated for relevant experience/expertize in Gynecology & Obstetrics.
6	Members list of IRB (names, designations & qualifications) provided.
7	Summary of Protocol (Purpose of Trial) provided
8	Summary of Investigator's Brochure (IP, Vancomycin, CapScan) provided
9	Names of Monitors and Clinical Research Associate: FHI Clinical Inc. had been selected by BMGF as a monitor for this trial.
10	GMP Certificates duly issued by regulatory authority: i. Manufacturer of Vancomycin: Not provided ii. Manufacturer of VE818: Not provided (Only statement is attached) iii. Manufacturer of Placebo: Not provided (Only statement is attached) **Statement: As clinical stage manufacturer, Vedanta Biosciences has not been inspected by the US FDA** ISO Certificates for following companies: i. Manufacturer of CapScan: Not provided (Only statement is attached) **Subject: Company statement regarding the non-significant risk status of the CapScan intestinal collection device.** ii. Manufacturer of Stool collection tube: ISO 13485:2016 No. 2247783, Valid till 01-07-2025, Declaration of Conformity iii. Manufacturer of Saliva collection kit: ISO 13485:2016 No. FM 567041, Valid till 10-01-2026, Declaration of Conformity
11	Provide CoPP (Certificate of Pharmaceutical Product) or Free Sale Certificate or regulatory status for following products, duly issued by regulatory authority. i. CoPP/FSC of **Vancomycin 250mg capsule** provided (Certificate No. ZQJQ-GEQX, Valid till 22-08-2026). However, CoPP/FSC of **Vancomycin 125mg capsule** not provided. ii. **VE818:** Not provided iii. **CapScan:** Not provided iv. **Placebo:** Not provided v. **Stool collection tube:** Not provided vi. **Saliva collection kit:** Not provided
12	Provide label of Investigational Product. **Vancomycin 250mg** = Provided (**Vancomycin 125mg** = Not Provided) **VE818** = Provided **Placebo** = Provided
14	Authorization of sponsor to the principal investigator/institution for the conduct of clinical trial provided.
14	Insurance details (medical treatment cost in case of any SAE and compensation in case of any fatality) of subjects not provided.
15	List of tests to be conducted outside Pakistan with justifications and SOP for the transportation for Biological samples is provided. However, they have not provided the names of laboratories along with the details (Names with address, approval status in respective country, available testing facilities).
16	Approval of following documents from IRB & NBC missing: i. Core Protocol, Version 1.1, Date 03-05-2024 ii. Screening Permission Consent Form (English) V 1.1 iii. Project Screening Permission Consent Form (Sindhi) V 1.1 iv. Enrolment Consent Form (English) V 1.1 v. Enrolment Consent Form (Sindhi) for observational group V 1.1 vi. Enrolment Consent Form (English) for observational group V 1.1

7. The case was presented before the CSC.

Decision: The CSC after deliberation observed that there are a number of shortcomings in the application and decided to defer the case for communication of shortcomings to the applicant as discussed.

8. Accordingly, the CSC decision was communicated on 02nd December 2024, still response is awaited.

9. The case was placed before the Committee for consideration. The Committee decided the case as under:

Decision: The CSC after deliberation decided to defer the case for fulfilment of the shortcomings/deficiencies communicated on 02nd December 2024.

10. Accordingly, the CSC decision was communicated to applicant vide letter No. 16-53/2024-CT dated 09th January 2025, yet response is awaited.

11. In reply to DRAP's letter No. 16-53/2024-CT dated 09th January 2025, Prof. Dr. Syed Asad Ali, Chair, Department of Community Health Sciences, Associate Dean Research, MC-Pakistan, Professor of Pediatrics and Community Health Sciences, Aga Khan University, Karachi & Dr. Saeed Hamid, Director CTU, Aga Khan University, Karachi submitted their response vide letter No. Nil dated 17-01-2025.

12. Their response to DRAP's queries is reproduced as follows:

Sr. No.	DRAP queries	Aga Khan University response
1	Following data related to VE-818 is provided: d. Authentic pre-clinical studies (provided) and data of Phase-I trial (JNJ-67670187) e. Toxicity studies (including reproductive toxicology (not conducted), Genotoxicity studies (not conducted), Carcinogenicity studies (not conducted), Mutagenic studies (not conducted), Teratogenic studies (not conducted) and other Pharmacokinetic data including dosage selection (not conducted). f. Antigenicity and immunogenicity studies (not conducted).	**Toxicity Studies:** Due to the commensal nature of the bacteria comprising VE818 and the lack of appropriate animal models that can mimic the interactions between the microbiome and its host, traditional toxicology studies were not conducted and have not been requested by any regulatory agency for Vedanta's live bio-therapeutic products (LBPs). Characterization of each individual bacterial strain in the LBP is required to build a product safety profile. This includes antibiotic-susceptibility, presence of virulence and antibiotic-resistance genes (ARG) and assessing the risk of genetic mobility. This approach is supported by interactions with the FDA and the EMA in the setting of other investigational LBPs from Vedanta and it is well established in the field. All 11 bacterial species in VE818 have not been associated with infection, were resistant to multiple antibiotics from various antibiotic classes and did not contain any virulence factors or clinically relevant ARGs in their genomes. Taken together, this evidence points towards a favorable safety profile. Importantly, VE818 showed no overt toxicity in mice, and it was shown to be safe and well-tolerated in healthy adults. **Reproductive Toxicology:** There are no appropriate animal models for reproductive toxicology evaluation in the context of LBPs. Therefore, safety in pregnancy was assessed by evaluating the prevalence and abundance of VE818-related species in pregnant women across various geographies including Pakistan. This analysis showed that VE818 species are common members of the microbiome of healthy pregnant women and therefore, carry minimal risk. Supporting this, data from the Alliance for Maternal and Newborn Health Improvement (AMANHI) study conducted in pregnant women from Pakistan showed that VE818-species were correlated with positive pregnancy outcomes (study attached-Annexure 2). **Genotoxicity:** Genotoxicity studies have not been conducted and have not been requested for any regulatory agency for Vedanta's LBPs. Bacteria do not have the same distribution properties as small molecules and therefore are not expected to interact with DNA. **Carcinogenicity, Mutagenic, and Teratogenic Studies:** No carcinogenicity, mutagenic and teratogenic studies have been conducted and have not been requested for any regulatory agency for Vedanta's LBPs. The organisms in VE818 represent commensal bacteria residing within a healthy human intestinal microbiota and do not have known carcinogenic, mutagenic or teratogenic potential. **Pharmacokinetic Data and Dosage Selection:** Classical pharmacokinetic studies are not applicable to this type of product. However, in healthy volunteers daily doses of VE818 for 14 days after vancomycin pretreatment was the most optimal dose leading to VE818 intestinal colonization for several weeks, which is key for efficacy. A short course of Vancomycin before VE818 was required for abundant

		and durable colonization, even at high doses (RTR-0027). In this Phase 1 study, VE818 was well-tolerated with few side effects, mainly gastrointestinal symptoms. **Antigenicity and Immunogenicity Studies:** The safety profile of VE818 indicates minimal risk of antigenicity. The strains in VE818 are normal commensal organisms found in the human GI tract and have been shown to be prevalent and abundant within the maternal microbiome. In the intestine, they have been demonstrated to stimulate a population of FoxP3+CD4+ Treg cells in the colonic mucosa and augment the production of secondary bile acids. These Treg cells and metabolites are associated with the clinical effect of reducing colonic inflammation in mouse models of colitis.
2	Safety and Performance studies of CapScan Medical Device in pregnant women: The device was used in EMP I trail which is approved by DRAP.	Already provided
3	Safety studies of Vancomycin in pregnant women: Pregnancy B category drug	Already provided
4	As per submitted documents, proposed clinical trial steps like screening, ICF, administration of LPs and collection of samples (pre and post administration) will be conducted at antenatal clinics / homes from different union councils of Matiari District. As per Bio Study Rules 2017, Trial procedures can be done only at licensed clinical trial site(s). Furthermore, Matiari site (Matiari Research & Training Center, Matiari operated under AKU) is not approved for above mentioned Clinical Study (Phase-II).	The proposed clinical trial processes including screening, ICF, initial administration of LPs, ultrasounds will be conducted at the research site of Matiari Research & Training Center, operated under AKU. The center has license CTS-0035 to act as Clinical Trial Site by DRAP which has expired, and its renewal application has been submitted to DRAP (No. F. 15-35/2020-DD(PS)
5	Provided CVs evaluated for relevant experience/expertize in Gynecology & Obstetrics.	Already provided
6	Members list of IRB (names, designations & qualifications) provided.	Already provided
7	Summary of Protocol (Purpose of Trial) provided	Already provided
8	Summary of Investigator's Brochure (IP, Vancomycin, CapScan) provided	Already provided
9	Names of Monitors and Clinical Research Associate: FHI Clinical Inc. had been selected by BMGF as a monitor for this trial.	Already provided
10	GMP Certificates duly issued by regulatory authority: i. Manufacturer of Vancomycin: Not provided ii. Manufacturer of VE818: Not provided (Only statement is attached) iii. Manufacturer of Placebo: Not provided (Only statement is attached) **Statement: As clinical stage manufacturer, Vedanta Biosciences has not been inspected by the US FDA** ISO Certificates for following companies: ii. Manufacturer of CapScan: Not provided (Only statement is attached) **Subject: Company statement regarding the non-significant risk status of the CapScan intestinal collection device.** ii. Manufacturer of Stool collection tube: ISO 13485:2016 No. 2247783, Valid till 01-07-2025, Declaration of Conformity iii. Manufacturer of Saliva collection kit: ISO 13485:2016 No. FM 567041,	In the United States, the regulatory body, the Food and Drug Administration (FDA) does not issue good manufacturing practices (GMP) certificates or manufacturing licenses to clinical or commercial manufacturing facilities. The FDA oversees and regulates commercial drug manufacturing through inspections of commercial registered establishments to ensure adherence current GMP regulations. Currently, Vedanta does not manufacture commercial products and thus has not been inspected by the FDA. Vedanta is located in the state of Massachusetts, within the United States. Please find our US Massachusetts Qualification Certificate stating Vedanta is a legal entity qualified to do business. Additionally, please find a QP certificate for VE202 that has been included to this submission (Annexure 3). Vedanta has undergone an audit by a European Union (EU) Qualified Person (QP) for the release of other drug products into the EU, including VE202. The 11 strains present in VE818 are also part of the VE202 consortium and are manufactured from the same cell banks. VE818 has not been used in clinical trials within the EU, and therefore, a QP certificate has not been issued for this product. Annexure 3: a. The GMP Statement for Vancomycin is attached b. The NDA (New Drug Application) and NDA status for Vancomycin is attached. c. The GMP for VE818 is attached. d. The GMP for Placebo is attached. e. Certificate of Registration, Certificate of Compliance and Certificate of Action for Capscan device are attached.

	Valid till 10-01-2026, Declaration of Conformity	f. Company statement regarding NSR for Capscan device is attached.
11	Provide CoPP (Certificate of Pharmaceutical Product) or Free Sale Certificate or regulatory status for following products, duly issued by regulatory authority. vii. CoPP/FSC of **Vancomycin 250mg capsule** provided (Certificate No. ZQJQ-GEQX, Valid till 22-08-2026). However, CoPP/FSC of **Vancomycin 125mg capsule** not provided. viii. **VE818:** Not provided ix. **CapScan:** Not provided x. **Placebo:** Not provided xi. **Stool collection tube:** Not provided xii. **Saliva collection kit:** Not provided	A. We are not using product Vancomycin 125mg B. Vedanta is located in the state of Massachusetts, within the United States. Please find our US Massachusetts Qualification Certificate stating Vedanta is a legal entity qualified to do business. Additionally, please find a QP certificate for VE202 that has been included to this submission. Vedanta has undergone an audit by a European Union (EU) Qualified Person (QP) for the release of other drug products into the EU, including VE202. The 11 strains present in VE818 are also part of the VE202 consortium and are manufactured from the same cell banks. VE818 has not been used in clinical trials within the EU, and therefore, a QP certificate has been issued for this product (Annexure 3). C. The stool collection tube and saliva collection tube are simply 2ml and6ml plastic tubes respectively hence CoPP or FSC are not available. However, the declaration of conformity is attached and ISO certificates are attached. (Annexure4) Annexure 4: a. The certificate to do business in the Commonwealth is attached. b. Free sale certificate for CAPSCAN is attached. c. Declaration of Conformity for stool kit is attached. d. Declaration of Conformity for saliva kit is attached.
12	Provide label of Investigational Product. **Vancomycin 250mg** = Provided (**Vancomycin 125mg** = Not Provided) **VE818** = Provided **Placebo** = Provided	We are not using product Vancomycin 125mg
13	Authorization of sponsor to the principal investigator/institution for the conduct of clinical trial provided.	Already provided
14	Insurance details (medical treatment cost in case of any SAE and compensation in case of any fatality) of subjects not provided.	All of our trial participants are covered under insurance (insurance email attached-Annexure-5). Compensation details are provided in protocol section 23.0 (page 50) and in trial consent it is covered in possible risks and discomfort heading (page 6).
15	List of tests to be conducted outside Pakistan with justifications and SOP for the transportation for Biological samples is provided. However, they have not provided the names of laboratories along with the details (Names with address, approval status in respective country, available testing facilities).	The name and the complete address of the laboratory where certain tests will be performed are below: Name & Address: Suchitra Hourigan, MD Investigator, Lasker Clinical Research Scholar Chief, Clinical Microbiome Unit (CMU) Laboratory of Host Immunity and Microbiome National Institute of Allergy and Infectious Diseases National Institutes of Health Building 50, Rm 5511 50 South Dr. Bethesda, MD, 20892 United States of America. Available testing facilities: • Metatranscriptomics • Proteomics • Cell Harvesting • Metagenomics • Metabolomics • PAX Gene • IgG Sequencing
16	Approval of following documents from IRB & NBC missing: vii. Core Protocol, Version 1.1, Date 03-05-2024 viii. Screening Permission Consent Form (English) V 1.1 ix. Project Screening Permission Consent Form (Sindhi) V 1.1 x. Enrolment Consent Form (English) V 1.1 xi. Enrolment Consent Form (Sindhi) for	Approval Letters for the IRB and NBC are attached. (Annexure-6)

	observational group V 1.1 xii. Enrolment Consent Form (English) for observational group V 1.1	
17	Notification and Composition of DSMB	DSMB charter is attached. (Annexure-7)

Sr. No.	Evaluator Remarks
1	Following data related to VE-818 is provided: g. Authentic pre-clinical studies (provided) and data of Phase-I trial (JNJ-67670187) h. Toxicity studies (including reproductive toxicology (not conducted), Genotoxicity studies (not conducted), Carcinogenicity studies (not conducted), Mutagenic studies (not conducted), Teratogenic studies (not conducted) and other Pharmacokinetic data including dosage selection (not conducted). i. Antigenicity and immunogenicity studies (not conducted).
2	Safety and Performance studies of CapScan Medical Device in pregnant women: The device was used in EMP I trail which is approved by DRAP.
3	Safety studies of Vancomycin in pregnant women: Pregnancy B category drug
4	Matiari site (Matiari Research & Training Center, Matiari operated under AKU) is not approved for above mentioned Clinical Study (Phase-II).
10	GMP Certificates duly issued by regulatory authority: i. Manufacturer of Vancomycin: Not provided ii. Manufacturer of VE818: Not provided (Only statement is attached) iii. Manufacturer of Placebo: Not provided (Only statement is attached) **Statement: As clinical stage manufacturer, Vedanta Biosciences has not been inspected by the US FDA** ISO Certificates for following companies: iii. Manufacturer of CapScan: Not provided (Only statement is attached) **Subject: Company statement regarding the non-significant risk status of the CapScan intestinal collection device.** ii. Manufacturer of Stool collection tube: ISO 13485:2016 No. 2247783, Valid till 01-07-2025, Declaration of Conformity iii. Manufacturer of Saliva collection kit: ISO 13485:2016 No. FM 567041, Valid till 10-01-2026, Declaration of Conformity
11	Provide CoPP (Certificate of Pharmaceutical Product) or Free Sale Certificate or regulatory status for following products, duly issued by regulatory authority. i. **CapScan:** provided ii. **Stool collection tube:** Not provided iii. **Saliva collection kit:** Not provided
16	Approval of following documents from IRB is attached: i. MPIGH2-ver 1.1 03-05-2024 -sa ii. SAP_EMP_II_02.11.23_Berry_01.25.24_FINALV2 (Version 0.2) iii. 01. Screening Consent Form English-V1.1-03-05-2024-sa (Version 1.1) iv. 01. Screening Consent Form Sindhi-V1.1-03-05-2024 (Version 1.1) v. 05. Trial Consent form English-V1.1-03-05-2024-sa (Version 1.1) vi. 05. Trial Consent form Sindhi-V1.1-03-05-2024 (Version 1.1) vii. 23. Trial Consent form English (for observational group) --V1.1-03-05-2024 (Version 1.1) viii. 23. Trial Consent form Sindhi (for observational group) -V1.1-03-05-2024 (Version 1.1) Approval of following document from NBC is attached (No. 4-87/NBCR-1050/23/1774 dated 24-05-2025): i. Core Protocol, Version 1.1, Date 03-05-2024 **Approval of following documents from NBC is missing:** **i. Screening Consent Form English-V1.1-03-05-2024-sa (Version 1.1)** **ii. Screening Consent Form Sindhi-V1.1-03-05-2024 (Version 1.1)** **iii. Trial Consent form English-V1.1-03-05-2024-sa (Version 1.1)** **iv. Trial Consent form Sindhi-V1.1-03-05-2024 (Version 1.1)** **v. Trial Consent form English (for observational group) --V1.1-03-05-2024 (Version 1.1)** **vi. Trial Consent form Sindhi (for observational group) -V1.1-03-05-2024 (Version 1.1)**
17	Data and Safety Monitoring Board (DSMB) charter is evaluated. Following are the key features: The MPIGH-2 Trial will be managed by two committees: i. Trial Management Group (TMG) ii. Data and Safety Monitoring Board (DSMB) The DSMB Charter (as per Core Protocol 2.1) describes its (a) Composition (b) Authority (c) Responsibilities. The composition is as follows: Prof. Sarah Saleem Prof. Somwe wa Somwe Dr. Hermann Lanou Prof. Shariful Alam Jilani **It is pertinent to mention here that DSMB Charter is as per Core Protocol 2.1. However, proposed PI has submitted Core Protocol, Version 1.1, Dated 03-05-2024.**

13. The case was placed before the Committee for consideration. The Committee decided the case as under:

Decision:

The CSC after deliberation and considering the response of the applicant deferred the case for fulfilment of shortcomings and approval of proposed trail site (Matiari Research & Training Center, Matiari operated under AKU) for the conduct of Phase-II clinical trials.

14. Accordingly, the CSC Decision was communicated on 04th February 2025. Reply from applicant received on 26th February and reproduced as follows:

Subject: ***Approval of clinical trial titled "Ability of the VE818 to reduce enteropathogen colonization and improve environmental enteropathy in pregnant women: a proof-of-concept and Phase-II randomized, placebo-controlled trial in Bangladesh, Pakistan, Zambia, and Burkina Faso" and Import permission for VE818, Vancomycin, placebo, and fecal sample collection device (CapScan). F.No.03-62/2024-CT (PS)***

Dear Sir,
Thank you for your letter, F.No.03-62/2024-CT (PS) dated 18-02-2025 in response to our application. The responses to the shortcomings mentioned in that letter are listed below.

I am also writing to formally request an amendment in the protocol of this study titled "Ability of VE818 to reduce enteropathogen colonization and improve environmental enteropathy in pregnant women: a proof of concept and phase II randomized placebo-controlled trial in Bangladesh, Pakistan, Zambia and Burkina Faso" which was last amended on 23-11-2024 as version 1.2.

The IRB approval for this amendment, highlighted version of amended protocol, summary of changes and updated trial documents are attached (Annexure 1). Moreover, NBC approval is pending and will be shared with DRAP as soon as available.

Sr.No.	DRAP Comments	Responses
1	*Following data related to VE-818 is provided:* *a. Authentic pre-clinical studies (provided) and data of Phase-I trial (JNJ-67670187)* *b. Toxicity studies (including reproductive toxicology (not conducted), Genotoxicity studies (not conducted), Carcinogenicity studies (not conducted), Mutagenic studies (not conducted), Teratogenic studies (not conducted) and other Pharmacokinetic data including dosage selection (not conducted).* *c. Antigenicity and immunogenicity studies (not conducted).*	***Toxicity Studies:*** *Due to the commensal nature of the bacteria comprising VE818 and the lack of appropriate animal models that can mimic the interactions between the microbiome and its host, traditional toxicology studies were not conducted and have not been requested by any regulatory agency for Vedanta's live biotherapeutic products (LBPs). Characterization of each individual bacterial strain in the LBP is required to build a product safety profile. This includes antibiotic-susceptibility, presence of virulence and antibiotic-resistance genes (ARG) and assessing the risk of genetic mobility. This approach is supported by interactions with the FDA and the EMA in the setting of other investigational LBPs from Vedanta and it is well established in the field. All 11 bacterial species in VE818 have not been associated with infection, were resistant to multiple antibiotics from various antibiotic classes and did not contain any virulence factors or clinically relevant ARGs in their genomes. Taken together, this evidence points towards a favorable safety profile. Importantly, VE818 showed no overt toxicity in mice, and it was shown to be safe and well-tolerated in healthy adults.* ***Reproductive Toxicology:*** *There are no appropriate animal models for reproductive toxicology evaluation in the context of LBPs. Therefore, safety in pregnancy was assessed by evaluating the prevalence and abundance of VE818-related species in pregnant women across various geographies including Pakistan. This analysis showed that VE818 species are common members of the microbiome of healthy pregnant women and therefore, carry minimal risk. Supporting this, data from the Alliance for Maternal and Newborn Health Improvement (AMANHI) study conducted in pregnant women from Pakistan showed that VE818-species were correlated with positive pregnancy outcomes (study already shared).* ***Genotoxicity:*** *Genotoxicity studies have not been conducted and have not been requested for any regulatory agency for Vedanta's LBPs. Bacteria do not have the same distribution properties as small molecules and therefore are not expected to interact with DNA.* ***Carcinogenicity, Mutagenic, and Teratogenic Studies:*** *No carcinogenicity, mutagenic and teratogenic studies have been conducted and have not been requested for any regulatory agency for Vedanta's LBPs. The organisms in VE818 represent commensal bacteria residing within a healthy human intestinal microbiota and do not have known carcinogenic, mutagenic or teratogenic potential.* ***Pharmacokinetic Data and Dosage Selection:*** *Classical pharmacokinetic studies are not applicable to this type of product. However, in healthy volunteers 14 daily doses of VE818 after vancomycin pretreatment was the most optimal dose leading to VE818 intestinal colonization for several weeks, which is key for efficacy. A short course of Vancomycin before VE818 was required for abundant and durable colonization, even at high doses (RTR-0027). In this Phase 1 study, VE818 was well-tolerated with few side effects, mainly gastrointestinal symptoms.* ***Antigenicity and Immunogenicity Studies:*** *The safety profile of VE818 indicates minimal risk of antigenicity. The strains in VE818 are normal commensal organisms found in the human GI tract and have been shown to be prevalent*

		intestine, they have been demonstrated to stimulate a population of FoxP3+CD4+ Treg cells in the colonic mucosa and augment the production of secondary bile acids. These Treg cells and metabolites are associated with the clinical effect of reducing colonic inflammation in mouse models of colitis.
2	*Safety and Performance studies of CapScan Medical Device in pregnant women: The device was used in EMP I trail which is approved by DRAP.*	*Already Provided*
3	*Safety studies of Vancomycin in pregnant women: Pregnancy B category drug*	*Already Provided*
4	*Matiari site (Matiari Research & Training Center, Matiari operated under AKU) is not approved for above mentioned Clinical Study (Phase-II).*	*Application for Phase-II trial specific license of Matiari site (Matiari Research & Training Center, Matiari operated under AKU) has been submitted and responses to DRAP queries over this application under letter No.F.15-35/2020-DD (P.S) have also been submitted on 21-02-2025.*
10	*GMP Certificates duly issued by regulatory authority:* *i. Manufacturer of Vancomycin: Not provided* *ii. Manufacturer of VE818: Not provided (Only statement is attached)* *iii. Manufacturer of Placebo: Not provided (Only statement is attached)* ***Statement: As clinical stage manufacturer, Vedanta Biosciences has not been inspected by the US FDA*** *ISO Certificates for the following companies:* *i. Manufacturer of CapScan: Not provided (Only statement is attached)*	*GMP Certificates: (Annexure 2)* *Manufacturer of Vancomycin: GMP Statement of ANI Pharmaceuticals is attached. Additionally, for Vancomycin NDA (New Drug Application) approval from Department of Health & Human Services, US is attached.* *Manufacturer of VE818: The statement of GMP compliance for Vedanta Biosciences is attached. In the United States, the regulatory body, the Food and Drug Administration (FDA) does not issue good manufacturing practices (GMP) certificates or manufacturing licenses to clinical or commercial manufacturing facilities. The FDA oversees and regulates commercial drug manufacturing through inspections of commercial registered establishments to ensure adherence to current GMP regulations. Currently, Vedanta does not manufacture commercial products and thus has not been inspected by the FDA.* *Manufacturer of Placebo: PCI Pharma services has declared Equivalent to EU GMP for placebo manufactured by Vedanta Biosciences (attached). Additionally, CoA of placebo is attached.* *ISO Certificates for the following companies:* *Manufacturer of CapScan: ISO certificate of Phoenix DeVentures, Inc., is attached.*
	Provide CoPP (Certificate of Pharmaceutical Product) or Free Sale Certificate or regulatory status for following products, duly issued by regulatory authority. *i.* ***CapScan:*** *Provided* *ii.* ***Stool collection tube:*** *Not provided* *iii.* ***Saliva collection kit:*** *Not provided*	*Free Sale certificate for Capscan is already provided.* *ii & iii. Stool collection tube and saliva collection tube are simple 2ml and 6ml plastic tubes respectively that do not require any CoPP or free sale certificate and can be procured locally in lab supplies.*
16	***Approval of the following documents from NBC is missing:*** ***iii. Screening Consent Form English V 1.1 -03-05-2024-sa (Version 1.1)*** ***iv. Screening Consent Form Sindhi V 1.1 -03-05-2024 (Version 1.1)*** ***v. Trial Consent Form English V 1.1 -03-05-2024-sa (Version 1.1)*** ***vi. Trial Consent Form Sindhi V 1.1 -03-05-2024 (Version 1.1)***	*The NBC approval for protocol amendments in Version 1.1 is attached. However, the NBC never specifies the document names being shared in their approval letters as IRB does. The initial approval of this study protocol version 1 is attached too for your reference. (Annexure 3)*

	*vii. **Trial Consent Form English (for observational group) V 1.1 -03-05-2024-sa (Version 1.1)*** *viii. **Trial Consent Form Sindhi (for observational group) V 1.1 -03-05-2024 (Version 1.1)***	
17	*Data and Safety Monitoring Board (DSMB) charter is evaluated. Following are the key features:* *i. Trial Management Group (TMG)* *ii. Data and Safety Monitoring Board (DSMB)* *The DSMB Charter (as per Core Protocol 2.1) describes its (a) Composition (b) Authority (c) Responsibilities.* *The composition is as follows:* *Professor Sarah Saleem* *Professor Somwe wa Somwe* *Dr Hermann Lanou* *Prof Shariful Alam Jilani* ***It is pertinent to mention here that DSMB Charter is as per Core Protocol 2.1. However, proposed PI has submitted Core Protocol, Version 1.1, Dated 03-05-2024.***	*The core protocol version 2.1 as mentioned in DSMB charter was an error.* *It is to clarify that based on the recent core protocol, 1.2 (dated: 23-11-204) is the correct version. For which updated DSMB charter is attached. (Annexure 4)* *The protocol amendment for version 1.2:* *Submitted to IRB on 27-01-2025 and its approval is attached.* *Submitted to NBC on 29-01-2025 and approval is awaited.* *Submitting to DRAP along with this letter.*

I appreciate your prompt attention to this matter and am available for any further information or clarification you may require.
Thank you for considering this application.

Best Regards,

15. Submitted for consideration and decision, please.

Case proceedings: -

The PI of the trial Dr. Asad Ali joined the meeting online (via Zoom link) and responded to the queries raised by the CSC members. The CSC observed that since this is a placebo-controlled trial and pretreatment with oral vancomycin (Pregnancy Cat. B) is required by the pregnant women posing the risk associated with taking an antibiotic during pregnancy. Responding to that the PI said that oral vancomycin is not absorbed systemically and in case of placebo the normal flora of intestine gets replenished in a few weeks after the use of antibiotic. It was also pointed out that during enrolment whether or not the subjects will be checked for the presence of bugs hypothesized to be responsible for malnutrition, in the gut of the pregnant mothers. The PI responded that testing will be done and at least 2 of the identified bugs need to be present in the microbiome as an inclusion criterion for enrolment of the subject. Justification for pretreatment with antibiotic for placebo arm was also sought. The expert members discussed to study the case in detail and present again in next CSC meeting.

Decision: -

The CSC after threadbare discussion decided to defer the clinical study for further deliberation.

16. The case was placed before the CSC for consideration. The Committee discussed the case and decided the case as under:

Proceedings:

The PI of the trial Prof, Dr. Asad Ali joined in-person along with Ms. Ammara Muzammil as requested by him. The PI presented trial details and responded to the queries raised by the CSC members. The PI was asked to submit clarification and documents for following observations:

i. NBC approval for protocol version 1.2.
ii. Phase-I Clinical trial data on "Ability of the VE818 to Reduce Enteropathogen Colonization and Improve Environmental Enteropathy in Pregnant Women".
iii. Clarification for statement regarding exemption of GMP inspection of the manufacturer of IMPs by US-FDA with relevant statutory provision.
iv. Current status of the regulatory approvals of trial in Bangladesh, Burkina Faso and Zambia. approvals.
v. If trial is initiated at any site/country, provide DSMB annual report of the trial.

Decision: The CSC after consideration deferred the case for provision of following clarification:

i. NBC approval for protocol version 1.2.
ii. Phase-I Clinical trial data on "Ability of the VE818 to Reduce Enteropathogen Colonization and Improve Environmental Enteropathy in Pregnant Women".
iii. Clarification for statement regarding exemption of GMP inspection of the manufacturer of IMPs by US-FDA with relevant statutory provision.
iv. Current status of the regulatory approvals of trial in Bangladesh, Burkina Faso and Zambia. approvals.
v. If trial is initiated at any site/country, provide DSMB annual report of the trial.

17. The applicant has submitted reply to the shortcomings vide letter dated 12th May, 2025, which is reproduced as under:

S. No.	DRAP Comments	Responses
1	NBC approval for protocol version 1.2	Attached in Annexure 1
2	Phase I Clinical trial data on "Ability of the VE8 I 8 to Reduce Enteropathogen Colonization and Improve Environn1ental Enteropathy in Pregnant Women"	Please find below our detailed response to the Authority's comment concerning the use of VE818 in pregnant women with Environmental Enteric Dysfunction (EEO) and malnutrition, while noting that the investigational product was originally developed with a focus on inflammatory bowel disease (IBO). We would like to respectfully highlight the following points in suppo1 1 of our trial application: **Phase 1 trial demonstrated a favorable safety and tolerability profile in healthy volunteers:** As outlined in the Phase 1 Clinical Study Report (Protocol 676701871BDI00I), VE818 (formerly JNJ- 67670187), a rationally designed consortium of beneficial Clostridia strains, was evaluated in healthy male and female participants across multiple dose levels and dosing regimens. The product was generally well tolerated, with no deaths, no discontinuations due to adverse events, and only a small number of serious adverse events, which were assessed as unrelated or unlikely to be related to the product. These findings suggest that VE818 may be suitable for fu l lher evaluation in other populations, including pregnant women, provided appropriate safeguards are in place. **I. The mechanism of action of VE818 is biologically relevant to EEO and maternal malnutrition:** VE818 is designed to support gut health by outcompeting bacterial pathogens and promoting colonic regulatory T-cell function-mechanisms that may help reduce intestinal inflammation and improve barrier integrity. While these effects have been primarily explored in the context of inflammatory

		bowel disease (IBO), they are also relevant to other enteric conditions. EEO shares several key pathophysiological features with IBO, including chronic mucosa! inflammation, microbial dysbiosis, high burden of enteric pathogens and impaired gut ba1Tier function. Given these similarities, it is scientifically reasonable to explore the potential utility of VE818 in EEO, and related conditions characterized by compromised gut health. In collaboration with the manufacturer, the Gates Foundation is working to ensure that, if proven effective, VE818 can be made accessible and affordable for all mothers affected by EEO. **2. The Phase 1 study was designed to evaluate general safety, not indication-specific efficacy:** As outlined in Point I, the Phase I trial for VE8 I 8 was conducted in healthy adult volunteers with the primary objective of assessing safety, tolerability, the requirement for antibiotic pre-treatment and phannacokinetics. This type of study is not indication-specific and is commonly used to establish a foundational safety profile that can inform further investigation in various populations and conditions. While VE818 was initially developed in the context of 18D, the safety data generated in healthy volunteers provides a rationale for evaluating the product in other settings where the mechanism of action is relevant and the potential benefit is high. It is our understanding based on FDA and EMA guidelines that regulatory fameworks support this stepwise approach, in which safety is established broadly before pursuing efficacy in specific target populations. This pathway is especially critical for advancing innovation in areas such as maternal and child health, where unmet needs are significant and therapeutic options are limited. **3.The proposed trial design includes appropriaterisk mitigation:** Our proposed study in pregnant women includes rigorous ethical oversight, close safety monitoring, and appropriate inclusion/exclusion criteria, all of which ensure that maternal and fetal health are prioritized. The risk-to-benefit ratio remains favorable in light of the unmet needs and the safety profile demonstrated in the Phase 1 trial. We hope this information helps clarify the scientific and ethical basis for the proposed use of VE8 I 8 in pregnant women with EED and malnutrition, in accordance with international research and regulatory standards.
3	Clarification for statement regarding exemption of GMP inspection of the manufacturer of !MPs by US-FDA with relevant statutory provision.	We appreciate DRAP's commitment to high standards of safety and quality and wish to clarify the regulatory status of VE818 and the acceptability of the GMP compliance documentation provided. Vedanta Biosciences does not hold a formal GMP certificate is U.S. Food and Drug Administration (FDA). This, however, is alignment with FDA practice, as the agency does not routinely certificates, particularly for

		investigational products that are nc for clinical trials in the U.S. and therefore not submitted under Investigational New Drug (IND) application. It is important to emphasize that Vedanta remains subject to full FDA oversight under U.S. law. Specifically: • The company is bound by the Federal Food, Drug, and Cosmetic Act (FDCA), including o Section 501(a)(2)(B) [21 U.S.C. §351 (a)(2)(B)], which deems a drugadulterated if it is not manufactured incompliance with current Good o Manufacturing Practices (cGMP); Section 704 [21 U.S.C. §374], which grants FDA inspection authority over any U.S.-based drug manufacturing facility. • Additionally, Vedanta's operations are subject to the cGMP requirements detailed in 21 CFR Parts 210 and 211, which apply to all human drug products, including those intended solely for export. In support of our application, we have enclosed two key documents from Vedanta Biosciences: I. **GMP Certificate for Active Biological Substance (VE818)** - Signed by Vedanta's Director of Quality Assurance, this document confirms that the VE818 active substance is manufactured in compliance with the GMP principles of: 0 U.S. FDA 21 CFR Parts 210, 211, 600, and 610; 0 European Directive 2001/20/EC; 0 PIC/S GMP Guide PE 009-11; 0 ICH Guidelines Q7, Q8, and Ql0. 2. **Statement of International GMP Compliance** - Signed by Vedanta's Vice President of Quality, this document attests that all operations, including manufacturing, warehousing, and quality control, adhere to FDA cGMP standards as well as international GMP norms, even though the product is not currently regulated under an IND. We also wish to inform you that the same investigational product, VE818, has been approved for clinical trial use by three other national regulatory authorities -in Bangladesh, Zambia, and Burkina Faso -after their independent review and acceptance of these GMP documents. We therefore respectfully request that DRAP accept the enclosed documentation as sufficient evidence of cGMP compliance. Approval of this clinical trial will ensure that Pakistani patients are included in high-quality global research efforts, with full assurance of manufacturing integrity and product safety.
4	Current status of the regulatory approvals of trial in Bangladesh, Burkina Faso and Zambia. approvals.	The regulatory approvals of trial in Bangladesh, Burkina Faso and Zambia are shared in Annexure 2.
5	If trial is initiated at any site/country, provide DSMB annual report of the trial	The DSMB meeting minutes of the initial meeting held on 27th February are shared in Annexure 3.

18. The applicant submitted reply and is reproduced as under:

S.No.	Response from applicant	DRAP Comments

1	NBC approval for protocol version 1.2 attached in Annexure 1	Seen
2	Please find below our detailed response to the Authority's comment concerning the use of VE818 in pregnant women with Environmental Enteric Dysfunction (EED) and malnutrition, while noting that the investigational product was originally developed with a focus on inflammatory bowel disease (IBD). We would like to respectfully highlight the following points in support of our trial application: **Phase 1 trial demonstrated a favorable safety and tolerability profile in healthy volunteers:** As outlined in the Phase 1 Clinical Study Report (Protocol 67670187IBD1001), VE818 (formerly JNJ-67670187), a rationally designed consortium of beneficial Clostridia strains, was evaluated in healthy male and female participants across multiple dose levels and dosing regimens. The product was generally well tolerated, with no deaths, no discontinuations due to adverse events, and only a small number of serious adverse events, which were assessed as unrelated or unlikely to be related to the product. These findings suggest that VE818 may be suitable for further evaluation in other populations, including pregnant women, provided appropriate safeguards are in place. **1. The mechanism of action of VE818 is biologically relevant to EED and maternal malnutrition:** VE818 is designed to support gut health by outcompeting bacterial pathogens and promoting colonic regulatory T-cell function—mechanisms that may help reduce intestinal inflammation and improve barrier integrity. While these effects have been primarily explored in the context of inflammatory bowel disease (IBD), they are also relevant to other enteric conditions. EED shares several key pathophysiological features with IBD, including chronic mucosal inflammation, microbial dysbiosis, high burden of enteric pathogens and impaired gut barrier function. Given these similarities, it is scientifically reasonable to explore the potential utility of VE818 in EED, and related conditions characterized by compromised gut health. In collaboration with the manufacturer, the Gates Foundation is working to ensure that, if proven effective, VE818 can be made accessible and affordable for all mothers affected by EED. **2. The Phase 1 study was designed to evaluate general safety, not indication-specific efficacy:** As outlined in Point 1, the Phase 1 trial for VE818 was conducted in healthy adult volunteers with the primary objective of assessing safety, tolerability, the requirement for antibiotic pre-treatment and pharmacokinetics. This type of study is not indication-specific and is commonly used to establish a foundational safety profile that can inform further investigation in various populations and conditions. While VE818 was initially developed in the context of IBD, the safety data generated in healthy volunteers provides a rationale for evaluating the product in other settings where the mechanism of action is relevant and the potential benefit is high. It is our understanding based on FDA and EMA guidelines that regulatory frameworks support this stepwise approach, in which safety is established broadly before pursuing efficacy in specific target populations. This pathway is especially critical for advancing innovation in areas such as maternal and child health, where unmet needs are significant and therapeutic options are limited. **3. The proposed trial design includes appropriate risk mitigation:** Our proposed study in pregnant women includes rigorous ethical oversight,	The goal of the treatment with JNJ-67670187 in clinical study 676701871BD1001 was to stimulate immune Treg cells in the colon to reduce the intestinal inflammation characteristic of UC and restore the gut microbiome to a healthy state both male and female. However, justification with scientific evidence is required to extrapolate the findings/results of that Phase-I study to pregnant females on given condition in a Phase-II study. The statement "The safety data generated in healthy volunteers provides rationale for evaluating the product in other setting where the mechanism of action is relevant and potential benefit is high" requires justification with scientific evidence when there is no Phase-I study conducted on pregnant females. Furthermore, what is the rationale based on regulatory frameworks established under FDA and EMA guidelines that strengthens this concept?

	close safety monitoring, and appropriate inclusion/exclusion criteria, all of which ensure that maternal and fetal health are prioritized. The risk-to-benefit ratio remains favorable in light of the unmet needs and the safety profile demonstrated in the Phase 1 trial. We hope this information helps clarify the scientific and ethical basis for the proposed use of VE818 in pregnant women with EED and malnutrition, in accordance with international research and regulatory standards.	
3	We appreciate DRAP's commitment to high standards of safety and quality and wish to clarify the regulatory status of VE818 and the acceptability of the GMP compliance documentation provided. Vedanta Biosciences does not hold a formal GMP certificate issued by the U.S. Food Administration (FDA). This, however, is in full alignment with FDA practice, as the a not routinely issue GMP certificates, particularly for investigational products that are for clinical trials in the U.S. and therefore not submitted under an Investigational New application. It is important to emphasize that Vedanta remains subject to full FDA oversight under U.S. law. Specifically: • The company is bound by the **Federal Food, Drug, and Cosmetic Act (FDCA)**, including o **Section 501(a)(2)(B)** [21 U.S.C. §351(a)(2)(B)], which deems a drug adulterated if it is not manufactured in compliance with **current Good Manufacturing Practices (cGMP)**; o **Section 704** [21 U.S.C. §374], which grants FDA inspection authority over any U.S.-based drug manufacturing facility. • Additionally, Vedanta's operations are subject to the cGMP requirements detailed in **21 CFR Parts 210 and 211**, which apply to all human drug products, including those intended solely for export. In support of our application, we have enclosed two key documents from Vedanta Biosciences: 1. **GMP Certificate for Active Biological Substance (VE818)** – Signed by Vedanta's Director of Quality Assurance, this document confirms that the VE818 active substance is manufactured in compliance with the GMP principles of: o U.S. FDA 21 CFR Parts 210, 211, 600, and 610; o European Directive 2001/20/EC; o PIC/S GMP Guide PE 009-11; o ICH Guidelines Q7, Q8, and Q10. 2. **Statement of International GMP Compliance** – Signed by Vedanta's Vice President of Quality, this document attests that all operations, including manufacturing, warehousing, and quality control, adhere to FDA cGMP standards as well as international GMP norms, even though the product is not currently regulated under an IND. We also wish to inform you that the same investigational product, VE818, has been approved for clinical trial use by **three other national regulatory authorities** – in **Bangladesh, Zambia, and Burkina Faso** – after their independent review and acceptance of these GMP documents. We therefore respectfully request that DRAP accept the enclosed documentation as sufficient evidence of cGMP compliance. Approval of this clinical trial will ensure that Pakistani patients are included in high-quality global research efforts, with full assurance of manufacturing integrity and product safety.	Regulatory approval from US-FDA is not provided. Director QA or Vice President Quality, Vedanta Biosciences, USA are not authorized to issue statements on GMP Compliance under Code of Federal Regulations (CFR). Moreover, mentioned provision of FDCA either don't exist or are irrelevant to the matter under discussion.
4	The regulatory approvals of trial in Bangladesh, Burkina Faso and Zambia are shared in Annexure 2.	Trial is yet not started.
5	The DSMB meeting minutes of the initial meeting held on 27th February are shared in Annexure 3.	Trial is yet not started. Details of the minutes regarding trial design are not provided.

19. The case was placed before the CSC for consideration.

Proceedings:

Prof. Dr. Syed Asad Ali, Professor of Community Health Sciences and Pediatrics, Associate Dean Research, Professor of Pediatrics and Community Health Sciences, Aga Khan University Hospital, Karachi, joined the meeting through Zoom link and explained the trial design, technical aspects of the study. Regarding GMP status of the IMPs manufacturer i.e. M/s Vedanta Biosciences, the PI apprised the Committee that US-FDA does not issue GMP certificate for the therapeutic goods manufacture for export purpose only. The CSC recommended that the statement of the PI may be confirmed from US-FDA through official correspondence. The PI was informed that, the GMP Certificate provided by is issued by the Director QA, which is not acceptable. The proposed trial site (i.e. Matiari Research Center) is not licensed to act as Clinical Trial Sites for the Clinical Trial. During discussion regarding participants' safety and study design it transpired that applicant has submitted a DSMB report, wherein, certain changes in the protocol have been recommended. The Committee directed the PI to submit the details of the proposed changes.

20. The Committee decided the case as under:

Decision:

The CSC after deliberation decided to defer the case for submission of following documents and clarifications:

i. **Status of manufacturer GMP issued by US-FDA.**
ii. **Details of protocol amendments suggested by DSMB.**
iii. **Trial Site approval by the CSC.**

2. The CSC further directed to confirm GMP status of the IMP manufacturer from US-FDA through email for confirmation that US-FDA does not issue GMP certificate for the therapeutic goods manufacture for export purpose only.

CASE No. 3.7:

APPLICATION FOR APPROVAL OF BIOEQUIVALENCE STUDY TITLED, "AN OPEN LABEL, BALANCED, RANDOMIZED, TWO TREATMENTS, TWO SEQUENCES, TWO PERIODS, SINGLE DOSE, CROSS OVER, BIOEQUIVALENCE STUDY OF TALOPEX (ESCITALOPRAM OXALATE) 20 MG TABLETS OF ABBOTT LABORATORIES VERSUS CIPRALEX (ESCITALOPRAM OXALATE) 20 MG TABLETS OF LUNDBECK INC., UNDER FASTING CONDITION IN HEALTHY HUMAN SUBJECTS", RECEIVED FROM M/S CENTER FOR BIOEQUIVALENCE STUDIES AND CLINICAL RESEARCH (CBSCR), ICCBS, UNIVERSITY OF KARACHI, KARACHI. F. NO.14-07/2025-BE (PS)

Application is received from Prof. Dr. M. Raza Shah, General Manager, Center for Biocquivalence Study and Clinical Research (CBSCR), University of Karachi, Karachi, dated 24th February 2025 for registration of subject Bioequivalence Study, under the Bio-Study Rules 2017, along with prescribed processing fee of Rs.245030/- deposited vide deposit slip number 0352359, dated 24th February 2025.

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

i. **Study title:** AN OPEN LABEL, BALANCED, RANDOMIZED, TWO TREATMENTS, TWO SEQUENCES, TWO PERIODS, SINGLE DOSE, CROSS OVER, BIOEQUIVALENCE STUDY OF TALOPEX (ESCITALOPRAM OXALATE) 20 MG TABLETS OF ABBOTT LABORATORIES VERSUS CIPRALEX (ESCITALOPRAM OXALATE) 20 MG TABLETS OF LUNDBECK INC., UNDER FASTING CONDITION IN HEALTHY HUMAN SUBJECTS.

ii. **Purpose of study:** AN OPEN LABEL, BALANCED, RANDOMIZED, TWO TREATMENTS, TWO SEQUENCES, TWO PERIODS, SINGLE DOSE, CROSS OVER, BIOEQUIVALENCE STUDY OF TALOPEX (ESCITALOPRAM OXALATE) 20 MG TABLETS OF ABBOTT LABORATORIES VERSUS CIPRALEX (ESCITALOPRAM OXALATE) 20 MG TABLETS OF LUNDBECK INC., UNDER FASTING CONDITION IN HEALTHY HUMAN SUBJECTS.

iii. **Investigational Product:** TALOPEX® (ESCITALOPRAM OXALATE) 20 MG TABLETS MANUFACTURED BY PHARMATEC PAKISTAN PVT. LTD. FOR ABBOTT LABORATORIES, Karachi.

iv. **Reference Product:** CIPRALEX® (ESCITALOPRAM OXALATE) 20 MG TABLETS OF LUNDBECK INC. DENMARK.

v. **Sponsor:** M/s ABBOT LABORATORIES 8TH FLOOR FAISAL HOUSE SHARH E FAISAL Karachi, PAKISTAN.

vi. **Principal Investigator:** Prof. Dr. Raza Shah, CNIC No. 422014178970-1, General Manager, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, Karachi.

vii. **Co-Principal Investigator:** Dr. Naghma Hashmi (Co-PI)

viii. **Funding Source**: M/s ABBOT LABORATORIES 8TH FLOOR FAISAL HOUSE SHARH E FAISAL Karachi, PAKISTAN.

ix. **Cost of the Project**: Rs.57,60,000/-.

x. **Subjects enrolment**: 24 VOLUNTEERS.

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

S. No.	Document	Remarks
1	Application on prescribed form-IIA.	Application on Form – IIA(amended) is provided.
2	Prescribed processing fee	Rs.245030/- deposited vide deposit slip number 0352359, dated 24th February 2025 (*The fee is not submitted on the prescribed fee challan*).
3	Name of Investigational Product (including all available names; trade, generic or INN name, chemical code, etc.,)	Attached. 1. **Investigational Product:** TALOPEX® (ESCITALOPRAM OXALATE) 20 MG TABLETS MANUFACTURED BY PHARMATEC PAKITAN Pvt. Ltd for ABBOTT LABORATORIES, Karachi. 2. **Reference Product:** CIPRALEX® (ESCITALOPRAM OXALATE) 20 MG TABLETS OF LUNDBECK INC. DENMARK
4	Dosage Form of Investigational Product	ATTACHED. TABLETS
5	Formulation of Investigational Product	INFORMATION LEAFLET (SMPC) IS PROVIDED
6	Pharmacodynamics and Pharmacokinetics of Investigational Product	ATTACHED.
7	Purpose of study defining the indication along with the anticipated cost of the project and sources of fund	ATTACHED. PURPOSE: TO DETERMINE BIOEQUIVALENCE OF TALOPEX (ESCITALOPRAM OXALATE) 20 MG TABLETS OF ABBOTT LABORATORIES VERSUS CIPRALEX (ESCITALOPRAM OXALATE) 20 MG TABLETS OF LUNDBECK INC., UNDER FASTING CONDITION IN HEALTHY HUMAN SUBJECTS. COST: 57,600,000 PKR SOURCE: M/S Abbot Labs. (Pak) Ltd.
8	Proposed center for the study	THE CENTER FOR BIOEQUIVALENCE STUDIES AND CLINICAL RESEARCH (CBSCR) INTERNATIONAL CENTER FOR CHEMICAL AND BIOLOGICAL SCIENCES (ICCBS) UNIVERSITY OF KARACHI, KARACHI. (BA/BE C-0002)
9	Investigational design and study plan	A SINGLE-CENTRE, OPEN-LABEL, RANDOMIZED, SINGLE-DOSE, TWO-PERIOD, TWO-WAY, CROSS-OVER STUDY. SUBJECTS WILL RECEIVE ONE SINGLE DOSE PER TREATMENT PERIOD SEPARATED BY A WASH-OUT

		PERIOD OF SEVEN (07) DAYS. BLOOD SAMPLES WILL BE TAKEN UP TO 48.0 HOURS POST-DOSE
10	Pre-clinical or clinical data or safety studies	Attached. *Need to be reviewed by CSC experts.
11	Final protocol	Attached. Protocol Number: ESTA-123-0337 Dated 06.09.2024 Version 1.0 *Need to be reviewed by CSC experts.
12	Detail of the investigator (Principal investigator, analysts, and others along with CV)	CVs of the following are attached: 1. Prof. Dr. M. Raza Shah (PI), General Manager, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, Karachi. (Page 79-83/Corr.) 2. Dr. Naghma Hashmi (Co-PI) (Page 84-88/Corr.) * PI's qualifications need to discussed
13	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached. IRB approval Ref. # Ref. # ICCBS/CBSCR/IEC/LET-006/2024 Date: 12-11-2024
14	Approval of National Bio-ethics Committee (NBC)	Attached. NBC approval Ref: No Ref: N o.4-87 /NBCR-1188/24/996, dated 09-01-2025 (for a period of one year).
15	BA/BE Study Site approval by DRAP	BA/BE -C-0002
16	Informed consent (English and Urdu)	Attached. *Need to be reviewed by CSC experts.
17	Summary of the protocol or synopsis (Investigational Product)	---
18	Adverse Event Reporting Form	Attached.
19	Name of the monitor or clinical research associate	---
20	Certificate of Analysis of Test Product and GMP Certificate or Drug Manufacturing License of the Manufacturer	Copy of GMP Certificate of M/s Pharmatec Pakistan (Pvt.) Ltd. D- 86/A S.I.T.E, Karachi is attached (expired on 06th September 2026). COA not provided DML not provided
21	Details regarding reference product (Country of origin, mode of purchase, shipment procedure) along with any other relevant documents if available	Tab Cipralex 20mg (Reg. No. 059035) Country of origin: **Denmark.** The mode of purchase will be: Direct Purchase (From Time Medicose, Karachi) Shipment procedure: ---
22	The proposed label of the investigational product	Attached
23	Quantity of an investigational product to be used in the study along with justification	**FOR REFERENCE PRODUCT** Sample Size=24 Investigational drug for clinical phase= 24 Tablets For Retention/Archiving= 3 times of study drug= 24x5 = 120 Tablets For Comparative Dissolution Profile=36*2=72 Tablets For Certificate of Analysis=50*2=100 Tablets Total no. of Tablets= For clinical phase +Retention /Archiving+ Comparative Dissolution Profile +COA=24+120+72+100= 316 Tablets. **FOR TEST PRODUCT** Sample Size=24 Investigational drug for clinical phase= 24 Tablets

		For Retention/Archiving= 3 times of study drug= 24x5 = 120 Tablets For Comparative Dissolution Profile=36*2=72 Tablets For Certificate of Analysis=50*2=100 Tablets Total no. of Tablets= For clinical phase +Retention /Archiving+ Comparative Dissolution Profile +COA=24+120+72+100= 316 Tablets.
24	Undertaking on affidavit	Attached. (Need to be provided again if PI changed)

04. After initial scrutiny the following shortcomings were observed:

i. Country of manufacturing site for the reference product is Denmark, whereas, it is submitted that it will be directly purchased from M/s Times Medicose Karachi (being registered in Pakistan).
ii. Drug Registration and CGMP for the investigational product is provided (M/s Pharmatech Pakistan Pvt. Ltd.) whereas the CoA and MA (M/s Abbot Laboratories Karachi) needs to be provided.
iii. The qualification of PI is not as per the conditions mentioned in the section 7.4 of the "Guidelines to Conduct Clinical Research in Pakistan".
iv. Formulation of the investigational product needs to be provided.
v. In the study protocol (Page.25of57) 7.1 (v) ***Inclusion Criteria,*** *says "Normal or insignificant ECG", clarification is sought regarding whether the performance and interpretation of ECG will be on site or otherwise.*
vi. In the study protocol (Page.32of57) 10.1.3.1 ***Subject Sample Analysis,*** *details regarding process validation for bioanalysis using LC-MS/MS need to be provided.*

(In order to avoid conflict of interest, the Secretary, CSC (being evaluator of the case) will not participate in voting.)

05. The case was placed before the CSC for consideration.

Decision: The CSC after deliberation decided to defer the case for submission of followings clarification:

i. **Country of manufacturing site for the reference product is Denmark, whereas, it is submitted that it will be directly purchased from M/s Times Medicose Karachi (being registered in Pakistan).**
ii. **Drug Registration and CGMP for the investigational product is provided (M/s Pharmatech Pakistan Pvt. Ltd.) whereas the CoA and MA (M/s Abbot Laboratories Karachi) needs to be provided.**
iii. **The qualification of PI is not as per the conditions mentioned in the section 7.4 of the "Guidelines to Conduct Clinical Research in Pakistan".**
iv. **Formulation of the investigational product needs to be provided.**
v. **In the study protocol 7.1 (v) Inclusion Criteria, says "Normal or insignificant ECG", clarification is sought regarding whether the performance and interpretation of ECG will be on site or otherwise.**
vi. **In the study protocol 10.1.3.1 Subject Sample Analysis, details regarding process validation for bioanalysis using LC-MS/MS need to be provided.**

2. The CSC further decided and delegate its powers to the Chairman CSC to decide the case accordingly after submission of above mention information.

6. Accordingly, the CSC decision was communicated to the applicant vide letter bearing No. 16-56/2025-CSC, dated 06th May 2025. The applicant has submitted the response to the shortcomings vide letter dated 12th May, 2025, which is reproduced as under:

Title""An open label, balanced, randomized, two treatments, two sequences, two periods, single dose, cross over, bioequivalence study of *Talopex*® (Escitalopram oxalate) 20 mg tablets of Abbott Laboratories versus Cipralex® (Escitalopram oxalate) 20 mg tablets of Lundbeck Inc., under fasting condition in healthy human subjects."

DRAP Short coming 1: Country of manufacturing site for the reference product is Denmark, whereas, it is submitted that it will be directly purchased from M/s Times Medicos Karachi (being registered in Pakistan).

PI's Response:
At M/s Time Medicos Karachi, Denmark manufactured Cipralex (Reference product) is available and hence reference product will be procured from M/s Time Medicos Karachi.
Purchasing site: M/s Time Medicos Karachi
Manufacturing Site: Lundbeck Inc.,Denmark

DRAP Short coming 2: Drug Registration and CGMP for the investigational product is provided (M/s Pharmatech Pakistan pvt. Ltd.) whereas the CoA and MA (M/s Abbot Laboratories Karachi) needs to be provided

PI's Response:
. CoA and MA are enclosed

DRAP Short coming 3:
The qualification of PI is not as per the conditions mentioned in the section 7 .4 of the "Guidelines to Conduct Clinical Research in Pakistan".

PI's Response:
As per the conditions mentioned in the section 7.4 of the "Guidelines to Conduct Clinical Research in Pakistan" for the qualification of PI "***Principal Investigator (PI) is the researcher, usually a doctor or other healthcare professional***" this statement doesn't show that the PI must be a physician.

Similarly, in the section 4 of the ICH-GCP E6R2 that stated, the regulations do not require that the investigator be a physician. The regulations require that sponsors select investigators who are qualified by training and experience as appropriate experts to investigate the drug. The regulations do not specify the minimum requirements nor do the regulations specify what qualifications an investigator must have in order to be considered qualified by training and experience to conduct a clinical investigation. Sponsors have discretion in determining what qualifications, training, and experience will be needed, based on the general recognition that this would include familiarity with human subject protection (HSP) regulations (i.e., 21 CFR Parts 50 and 56) and practices as well as good clinical practice (GCP) regulations (see 21 CFR Part 312) and standards (e.g., ICH E6) for the conduct of clinical studies.

According to the regulations Prof. Dr. Raza as PI of the study possess extensive experience. He conducted **ten** Toxicological Studies, **twenty-two** Bioequivalence (BE) and **six** Pharmacokinetic (PK) studies, **four** Phase-II Randomized Clinical Trial (RCT) on bronchitis, gastritis, pelvic inflammation and COVID-19 patients with traditional Chinese medicine for Safety and Efficacy evaluation as Principal Investigator (PI) and lead the one Phase-I RCT of Sinopharm COVID-19 vaccine and one Phase-III RCT of COVID-19 booster vaccine as country PI in Pakistan. **(List of studies are attached)**

1) The PI of this study has participated in a number of GCP and GLP training courses needed to act as PI. **(Training certificates of PI)**
2) The PI of this study has internationally published (Elsevier) four books in the area of Drug delivery which increased in depth of understanding of the drug interaction with the body and response of the body. The books are also available in Amazon and one of the book was declared best book of the year by HEC. The title of the books is given below i.e.

   I. Lipid-Based Nanocarriers for Drug Delivery and Diagnosis, **Paperback ISBN: 9780323527293**
   II. Nanocarriers for Cancer Diagnosis and Targeted Chemotherapy, **Paperback ISBN: 9780128167731**
   III. Metal Nanoparticles for Drug Delivery and Diagnostic Applications **Paperback ISBN: 9780128169605**
   IV. Nanocarriers for Organ-Specific and Localized Drug Delivery **Paperback ISBN:9780128210932**

3) The PI of the study also remained as Member in the panel of inspectors for Evaluation of Clinical Trial Sites from Drug Regulatory Authority of Pakistan (DRAP), Letters received from DRAP to act as inspector)
4) The PI of the study also Awarded with an **Edinburgh Certificate in Fellowship of Royal College of Physicians.**
5) The PI of the study also Awarded with an **International award for contribution to Chinese medicine achievement award in medical science** (2022)
6) The PI of the study also Awarded with certificate as an Expert Advisory Committee Member of the International Traditional Medicine Clinical Trial Registry
7) The PI of the study serve as a Visiting Professor of school of Pharmacy, Hunan University of Chinese Medicine

All the supporting documents are attached
DRAP Short coming 4: Formulation of the investigational product needs to be provided.
PI's Response: Attached
DRAP Short coming 5: In the study protocol 7.1 (v) Inclusion Criteria, says "Normal or insignificant ECG", clarification is sought regarding whether the performance and interpretation of ECG will be on site or otherwise.
PI's Response: The ECG will be recorded before check out of period II and the interpretations of ECG will be made by competent and skilled Cardiologist at same time before the checkout of study participants.
DRAP Short coming -6: In the study protocol 10.1.3.1 Subject Sample Analysis, details regarding process validation for bioanalysis using LC-MS/MS need to be provided.
PI's Response: Process validation are added in the same section 10.1.3.

7. The case was placed before the CSC for consideration.

Decision:

The CSC after deliberation decided to approve the Bio-Equivalence Study titled, "An Open Label, Balanced, Randomized, Two Treatments, Two Sequences, Two Periods, Single Dose, Cross Over, Bioequivalence Study of Talopex (Escitalopram Oxalate) 20 mg Tablets of Abbott Laboratories Versus Cipralex (ESCITALOPRAM OXALATE) 20 mg Tablets of Lundbeck Inc., under Fasting Condition in Healthy Human Subjects" to be conducted at the Center for Bioequivalence Studies and Clinical Research (CBSCR)-ICCBS, University of Karachi, University Road, Karachi. (BA/BE C-0002)

2. The Committee also approved following quantity of IMPs and auxiliary items to be imported/procured for the study:

- **REFERENCE PRODUCT (Cipralex (Escitalopram Oxalate) 20 mg Tablets of Lundbeck Inc.)**
  i. Sample Size=24
  ii. Investigational drug for clinical phase= 24 Tablets
  iii. For Retention/Archiving= 3 times of study drug= 24x5 = 120 Tablets
  iv. For Comparative Dissolution Profile=36*2=72 Tablets
  v. For Certificate of Analysis=50*2=100 Tablets
  vi. Total number of Tablets= For clinical phase +Retention /Archiving+ Comparative Dissolution Profile +COA=24+120+72+100 **= 316 Tablets.**

- **TEST PRODUCT (Talopex (Escitalopram Oxalate) 20mg Tablets, Manufactured by Abbott Laboratories, Karachi.)**
  i. Sample Size=24
  ii. Investigational drug for clinical phase= 24 Tablets
  iii. For Retention/Archiving= 3 times of study drug= 24x5 = 120 Tablets
  iv. For Comparative Dissolution Profile=36*2=72 Tablets
  v. For Certificate of Analysis=50*2=100 Tablets
  vi. Total number of Tablets= For clinical phase +Retention /Archiving+ Comparative Dissolution Profile +COA=24+120+72+100**= 316 Tablets.**

3. The Committee directed the PI to procure Test/Reference product directly from manufacturer or its importer and after procurement submit all documents as per Form-IIA (amended)

CASE No. 3.8:

APPLICATION FOR APPROVAL OF BIOEQUIVALENCE STUDY TITLED, "A SINGLE CENTER, OPEN LABEL, BALANCED, RANDOMIZED, SINGLE-DOSE, TWO- PERIOD, TWO-SEQUENCE, TWO-WAY, CROSS-OVER ORAL

BIOEQUIVALENCE STUDY COMPARING BRETILOR 90MG (TICAGRELOR) TABLET MANUFACTURED BY THE HORIZON HEALTHCARE (PVT) LTD WITH BRILINTA™ 90MG (TICAGRELOR) TABLET MANUFACTURED BY ASTRAZENECA IN HEALTHY, ADULT SUBJECTS UNDER FASTING CONDITION.", RECEIVED FROM M/S CENTER FOR BIOEQUIVALENCE STUDIES AND CLINICAL RESEARCH (CBSCR), ICCBS, UNIVERSITY OF KARACHI, KARACIII. F. NO.14-08/2025-BE (PS)

Application is received from Prof. Dr. M. Raza Shah, General Manager, Center for Biocquivalence Study and Clinical Research (CBSCR), University of Karachi, Karachi, dated 21st February 2025 for registration of subject Bioequivalence Study, under the Bio-Study Rules 2017, along with prescribed processing fee of Rs.245030/- deposited vide challan number 2574369276, dated 20th February 2025.

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

i. **Study title:** A SINGLE CENTER, OPEN LABEL, BALANCED, RANDOMIZED, SINGLE-DOSE, TWO- PERIOD, TWO-SEQUENCE, TWO-WAY, CROSS-OVER ORAL BIOEQUIVALENCE STUDY COMPARING BRETILOR 90MG (TICAGRELOR) TABLET MANUFACTURED BY THE HORIZON HEALTHCARE (PVT) LTD WITH BRILINTA™ 90MG (TICAGRELOR) TABLET MANUFACTURED BY ASTRAZENECA IN HEALTHY, ADULT SUBJECTS UNDER FASTING CONDITION.

ii. **Purpose of study:** A SINGLE CENTER, OPEN LABEL, BALANCED, RANDOMIZED, SINGLE-DOSE, TWO- PERIOD, TWO-SEQUENCE, TWO-WAY, CROSS-OVER ORAL BIOEQUIVALENCE STUDY COMPARING BRETILOR 90MG (TICAGRELOR) TABLET MANUFACTURED BY THE HORIZON HEALTHCARE (PVT) LTD WITH BRILINTA™ 90MG (TICAGRELOR) TABLET MANUFACTURED BY ASTRAZENECA IN HEALTHY, ADULT SUBJECTS UNDER FASTING CONDITION.

iii. **Investigational Product:** Bretilor 90mg (Ticagrelor) Tablet manufactured by The Horizon Healthcare (Pvt) Ltd Lahore.

iv. **Reference Product:** Brilinta 90mg (Ticagrelor) Tablet manufactured by AstraZeneca.

v. **Sponsor:** The Horizon Healthcare (Pvt) Ltd. Plot# 33 Sundar Industrial

vi. Estate, Lahore

vii. **Principal Investigator:** Prof. Dr. Raza Shah, General Manager, Center for Bioequivalence Study and Clinical Research (CBSCR), University of Karachi, Karachi.

viii. **Co-Principal Investigator:** Dr. Naghma Hashmi (Co-PI)

ix. **Funding Source**: The Horizon Healthcare (Pvt) Ltd. Plot# 33 Sundar Industrial Estate, Lahore.

x. **Cost of the Project**: Tentative cost 10,000,000 Rs

xi. **Subjects enrolment**: 44 SUBJECTS.

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

S. No.	Document	Remarks
1	Application on prescribed form-IIA.	Application on Form – IIA(amended) is provided.
2	Prescribed processing fee	Rs.245030/- deposited vide challan number 2574369276, dated 20th February 2025.
3	Name of Investigational Product (including all available names; trade, generic or INN name, chemical code, etc.,)	Attached. 1. **Investigational Product:** Bretilor 90mg (Ticagrelor) Tablet manufactured by The Horizon Healthcare (Pvt) Ltd Lahore 2. **Reference Product** Brilinta 90mg (Ticagrelor) Tablet manufactured by AstraZeneca
4	Dosage Form of Investigational Product	ATTACHED. TABLETS

5	Formulation of Investigational Product	ATTACHED. Product Name: Bretilor 90mg Tablet Master Formulation: Document No. MF/PRD/TAB-070 date 10-10-2023
6	Pharmacodynamics and Pharmacokinetics of Investigational Product	ATTACHED.
7	Purpose of study defining the indication along with the anticipated cost of the project and sources of fund	ATTACHED. PURPOSE: A single center, open label, balanced, randomized, single-dose, two- period, two-sequence, two-way, cross-over oral Bioequivalence study comparing Bretilor 90mg (Ticagrelor) Tablet manufactured by The Horizon Healthcare (Pvt) Ltd with BrilintaTM 90mg (Ticagrelor) Tablet manufactured by AstraZeneca in healthy, adult subjects under fasting condition. COST: Tentative cost 10,000,000 Rs SOURCE: he Horizon Healthcare (Pvt) Ltd. Plot# 33 Sundar Industrial Estate, Lahore.
8	Proposed center for the study	THE CENTER FOR BIOEQUIVALENCE STUDIES AND CLINICAL RESEARCH (CBSCR) INTERNATIONAL CENTER FOR CHEMICAL AND BIOLOGICAL SCIENCES (ICCBS) UNIVERSITY OF KARACHI, KARACHI. (BA/BE C-0002)
9	Investigational design and study plan	A single center, open-label, randomized, single-dose, two-period, two-way, cross-over study. Subjects will receive one single dose per treatment period separated by a wash-out period of seven (07) days. Blood samples will be taken up to 48.0 hours post-dose.
10	Pre-clinical or clinical data or safety studies	Attached. *Need to be reviewed by CSC experts.
11	Final protocol	Attached. Protocol No. CB(BABE)-053-TIC(B)-2024/Protocol/l .0 Dated 13.08.2024 Version 1.0 *Need to be reviewed by CSC experts.
12	Detail of the investigator (Principal investigator, analysts, and others along with CV)	CVs of the following are attached: 3. Prof. Dr. M. Raza Shah (PI), General Manager, Center for Bioequivalence Study and Clinical Research (CBSCR). University of Karachi, Karachi. 4. Dr. Naghma Hashmi (Co-PI) * PI's qualifications need to discussed
13	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	Attached. IRB approval Ref. # ICCBS/CBSCR/IEC/LET-005/2024 Date: 12-11-2024
14	Approval of National Bio-ethics Committee (NBC)	Attached. NBC approval Ref: Ref: No.4-87/NBCR-1187/24/995, dated 09-01-2025 (for a period of one year).
15	BA/BE Study Site approval by DRAP	BA/BE -C-0002
16	Informed consent (English and Urdu)	Attached. Doc. No# CB(BABE)-053-TIC(B)-2024/ICF(U)/J.0 Version Date: 13-08-2024 *Need to be reviewed by CSC experts.
17	Summary of the protocol or synopsis (Investigational Product)	---
18	Adverse Event Reporting Form	Attached.

19	Name of the monitor or clinical research associate	---
20	Certificate of Analysis of Test Product and GMP Certificate or Drug Manufacturing License of the Manufacturer	COA (Bretilor 90mg Tablets Batch No 07525 dated 12/02/2025.) DML provided GMP Certificate not provided
21	Details regarding reference product (Country of origin, mode of purchase, shipment procedure) along with any other relevant documents if available	Tab Brilinta 90mg (Reg. No. 059035) Country of origin: **USA.** Manufacturing Site: Turkey (SRA Country) The mode of purchase will be: Direct Purchase (From Time Medicose, Karachi) Shipment procedure: ---
22	The proposed label of the investigational product	Attached *Complete label is required
23	Quantity of an investigational product to be used in the study along with justification	**FOR REFERENCE PRODUCT** Sample Size=44 Investigational drug for clinical phase= 44 Tablets For Retention/Archiving= 3 times of study drug= 44x3 = 132 Tablets For Comparative Dissolution Profile=36*2=72 Tablets For Certificate of Analysis=50*2=100 Tablets Total no. of Tablets= For clinical phase +Retention /Archiving+ Comparative Dissolution Profile +COA=44+132+72+100= 348 Tablets. **FOR TEST PRODUCT** Sample Size=44 Investigational drug for clinical phase= 44 Tablets For Retention/ Archiving= 3 times of study drug= 44x3 = 132 Tablets For Comparative Dissolution Profile=36*2=72 Tablets For Certificate of Analysis=50*2=100 Tablets Total no. of Tablets= For clinical phase +Retention I Archiving+ Comparative Dissolution Profile +COA=44+132+72+100= 348 Tablets.
24	Undertaking on affidavit	Attached. (Need to be provided again if PI changed)

4. After initial scrutiny the following shortcomings were observed:
   i. Country of manufacturing site for the reference product is Turkey, whereas, it is submitted that it will be directly purchased from M/s Times Medicose Karachi.
   ii. CGMP for the investigational product needs to be provided.
   iii. The qualification of PI is not as per the conditions mentioned in the section 7.4 of the "Guidelines to Conduct Clinical Research in Pakistan".
   iv. In the study protocol (Page.11of45) ***FOR POST STUDY ASSESMENT,*** *says "ECG will be recorded before check out Period II....", clarification is sought regarding whether the performance and interpretation of ECG will be on site or otherwise.*
   v. In the study protocol (Page.11of45) ***BIO ANALYTICAL PROCEDURE,*** *details regarding the technique / process validation for bioanalysis need to be provided.*

(In order to avoid conflict of interest, the Secretary, CSC (being evaluator of the case) will not participate in voting.)

5. The case was placed before the CSC for consideration.

Decision: The CSC after deliberation decided to defer the case for submission of followings clarification:

i. Country of manufacturing site for the reference product is Turkey, whereas, it is submitted that it will be directly purchased from M/s Times Medicose Karachi.
ii. The t½ of the reference (parent) drug is 7 hours, whereas, that of an active metabolite is 9 hours. Clarification is sought regarding the bio-analysis for compilation of the kinetic study results.
iii. cGMP for the investigational product needs to be provided.

iv. **The metabolism of the drug is depending upon a liver enzyme (Cytochrome P3A4). Clarification is sought whether any LFT or baseline concentration of the said enzyme will be performed before the enrollment of the subject as it may vary among the population.**

v. **The qualification of PI is not as per the conditions mentioned in the section 7.4 of the "Guidelines to Conduct Clinical Research in Pakistan".**

vi. **In the study protocol FOR POST STUDY ASSESMENT, says "ECG will be recorded before check out Period II....", clarification is sought regarding whether the performance and interpretation of ECG will be on site or otherwise.**

vii. **In the study protocol BIO ANALYTICAL PROCEDURE, details regarding the technique / process validation for bioanalysis need to be provided.**

2. The CSC further decided and delegate its powers to the Chairman CSC to decide the case accordingly after submission of above mention information.

6. Accordingly, the CSC decision was communicated to applicant vide letter bearing No. 16-56/2025-CSC, dated 06th May 2025. The applicant has submitted the response to the shortcomings vide letter dated 12th May, 2025, which is reproduced as under:

Title"A single center, open label, balanced, randomized, single-dose, two- period, two-sequence, two-way, cross-over oral Bioequivalence study comparing Bretilor 90mg (Ticagrelor) Tablet manufactured by The Horizon Healthcare (Pvt) Ltd with Brilinta™ 90mg (Ticagrelor) Tablet manufactured by AstraZeneca in healthy, adult subjects under fasting condition."

DRAP Short coming 1: Country of manufacturing site for the reference product is Turkey, whereas, it is submitted that it will be directly purchased from M/s Time Medicos Karachi.
PI's Response: At M/s Time Medicos Karachi, Turkey manufactured Brilinta (Reference product) is available and hence reference product will be procured from M/s Kausar Medicos Karachi. Purchasing site: M/s Kausar Medicos Karachi Manufacturing Site: AstraZeneca Turkey
DRAP Short coming 2: The $t_{1/2}$ of the reference (parent) drug is 7 hours, whereas, that of an active metabolite is 9 hours. Clarification is sought regarding the bio-analysis for compilation of the kinetic study results.
PI's Response: To ensure accurate pharmacokinetic interpretation, the bioanalytical analysis include both analytes: • Quantify both Ticagrelor and its active metabolite separately. • Use validated LC-MS/MS methods with appropriate LLOQs for both. • Include enough time points post-dose (up to 48 hours typically) to define terminal elimination for both, particularly the longer-lived metabolite.
DRAP Short coming 3: CGMP for the investigational product needs to be provided.
PI's Response: CGMP is attached
DRAP Short coming 4: The metabolism of the drug is depending upon a liver enzyme (Cytochrome P3A4). Clarification is sought whether any LFT or baseline concentration of the said enzyme will be performed before the enrollment of the subject as it may vary among the population.
PI's Response: 1.Yes, LFTs will be performed before subject enrollment in clinical studies for drugs with hepatic metabolism. These tests assess liver health, and subjects with abnormal results will be typically excluded, as liver impairment could affect drug metabolism and skew the pharmacokinetic results. 2. No, measuring baseline CYP3A4 levels or activity is not typically required because the study is not focused on metabolism variability. 3. For more detailed metabolic analysis, genotyping or phenotyping may be added, but it's not part of standard

bioequivalence or routine PK studies.

DRAP Shortcoming 5: The qualification of PI is not as per the conditions mentioned in the section 7.4 of the "Guidelines to Conduct Clinical Research in Pakistan".

PI's Response:

As per the conditions mentioned in the section 7.4 of the "Guidelines to Conduct Clinical Research in Pakistan" for the qualification of PI "***Principal Investigator (PI) is the researcher, usually a doctor or other healthcare professional***" this statement doesn't show that the PI must be a physician.

Similarly, in the section 4 of the ICH-GCP E6R2 that stated, the regulations do not require that the investigator be a physician. The regulations require that sponsors select investigators who are qualified by training and experience as appropriate experts to investigate the drug. The regulations do not specify the minimum requirements nor do the regulations specify what qualifications an investigator must have in order to be considered qualified by training and experience to conduct a clinical investigation. Sponsors have discretion in determining what qualifications, training, and experience will be needed, based on the general recognition that this would include familiarity with human subject protection (HSP) regulations (i.e., 21 CFR Parts 50 and 56) and practices as well as good clinical practice (GCP) regulations (see 21 CFR Part 312) and standards (e.g., ICH E6) for the conduct of clinical studies.

According to the regulations Prof. Dr. Raza as PI of the study possess extensive experience. He conducted **ten** Toxicological Studies, **twenty-two** Bioequivalence (BE) and **six** Pharmacokinetic (PK) studies, **four** Phase-II Randomized Clinical Trial (RCT) on bronchitis, gastritis, pelvic inflammation and COVID-19 patients with traditional Chinese medicine for Safety and Efficacy evaluation as Principal Investigator (PI) and lead the one Phase-I RCT of Sinopharm COVID-19 vaccine and one Phase-III RCT of COVID-19 booster vaccine as country PI in Pakistan. **(List of studies are attached)**

8) The PI of this study has participated in a number of GCP and GLP training courses needed to act as PI. **(Training certificates of PI)**
9) The PI of this study has internationally published (Elsevier) four books in the area of Drug delivery which increased in depth of understanding of the drug interaction with the body and response of the body. The books are also available in Amazon and one of the book was declared best book of the year by HEC. The title of the books is given below i.e.

   V. Lipid-Based Nanocarriers for Drug Delivery and Diagnosis, **Paperback ISBN: 9780323527293**
   VI. Nanocarriers for Cancer Diagnosis and Targeted Chemotherapy, **Paperback ISBN: 9780128167731**

   VII. Metal Nanoparticles for Drug Delivery and Diagnostic Applications **Paperback ISBN: 9780128169605**
   VIII. Nanocarriers for Organ-Specific and Localized Drug Delivery **Paperback ISBN:9780128210932**

10) The PI of the study also remained as Member in the panel of inspectors for Evaluation of Clinical Trial Sites from Drug Regulatory Authority of Pakistan (DRAP), Letters received from DRAP to act as inspector)
11) The PI of the study also Awarded with an **Edinburgh Certificate in Fellowship of Royal College of Physicians.**
12) The PI of the study also Awarded with an **International award for contribution to Chinese medicine achievement award in medical science** (2022)
13) The PI of the study also Awarded with certificate as an Expert Advisory Committee Member of the International Traditional Medicine Clinical Trial Registry
14) The PI of the study serve as a Visiting Professor of school of Pharmacy, Hunan University of Chinese Medicine. All the supporting documents are attached

DRAP Short coming -6: In the study protocol ***FOR POST STUDY ASSESMENT***, "ECG will be recorded before check out period II.....", clarification is sought whether the performance and interpretation of ECG will be on site or otherwise.
PI's Response: The ECG will be recorded before check out of period II and the interpretations of ECG will be made by competent and skilled Cardiologist at same time before the checkout of study participants.
DRAP Short coming -7: In the study protocol ***BIO ANALYTICAL PROCEDURE,*** details regarding the technique process validation for bioanalysis need to be provided.
PI's Response: Details regarding the technique process validation for bioanalysis Response is mentioned on page no 38 of the protocol.

7. The case was placed before the CSC for consideration.

Decision:

The CSC after deliberation decided to approve the Bio-Equivalence Study titled, "A Single Center, Open Label, Balanced, Randomized, Single-Dose, Two- Period, Two-Sequence, Two-Way, Cross-Over Oral Bioequivalence Study Comparing Bretilor 90mg (Ticagrelor) Tablet Manufactured By The Horizon Healthcare (Pvt) Ltd with Brilinta™ 90mg (Ticagrelor) Tablet Manufactured By AstraZeneca In Healthy, Adult Subjects Under Fasting Condition." to be conducted at the Center for Bioequivalence Studies and Clinical Research (CBSCR)-ICCBS, University of Karachi, University Road, Karachi. (BA/BE C-0002)

2. The Committee also approved following quantity of IMPs and auxiliary items to be imported/procured for the study:

- **REFERENCE PRODUCT (Brilinta™ 90mg (Ticagrelor) Tablet Manufactured By AstraZeneca)**
  i. Sample Size=44
  ii. Investigational drug for clinical phase= 44 Tablets
  iii. For Retention/Archiving= 3 times of study drug= 44x3 = 132 Tablets
  iv. For Comparative Dissolution Profile=36*2=72 Tablets
  v. For Certificate of Analysis=50*2=100 Tablets
  vi. Total no. of Tablets= For clinical phase +Retention /Archiving+ Comparative Dissolution Profile +COA=44+132+72+100= **348 Tablets.**

- **TEST PRODUCT (Bretilor 90mg (Ticagrelor) Tablet manufactured by The Horizon Healthcare (Pvt) Ltd., Lahore.)**
  i. Sample Size=44
  ii. Investigational drug for clinical phase= 44 Tablets
  iii. For Retention/ Archiving= 3 times of study drug= 44x3 = 132 Tablets
  iv. For Comparative Dissolution Profile=36*2=72 Tablets
  v. For Certificate of Analysis=50*2=100 Tablets
  vi. Total no. of Tablets= For clinical phase +Retention I Archiving+ Comparative Dissolution Profile +COA=44+132+72+100= **348 Tablets.**

3. The Committee directed the PI to procure Test/Reference product directly from manufacturer or its importer and after procurement submit all documents as per Form-IIA (amended)

CASE No. 3.9:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED, "IMMUNOGENICITY AND SAFETY OF A RABIES VACCINE (SERUM-FREE VERO CELL), FREEZE-DRIED IN COMPARISON WITH VERORAB®, IN A SIMULATED POST-EXPOSURE PROPHYLAXIS REGIMEN IN HEALTHY POPULATIONS AGED

≥1 YEARS: A RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED PHASE III CLINICAL TRIAL". No. F. 03-70/2025-CT(PS)

Application Ref. No. Nil dated 21-04-2025 was received from Dr. **Ume Sughra**, **Principal Investigator** and **Al-Shifa Trust Eye Hospital, Jhelum Road, Rawalpindi** regarding subject cited above, wherein request they have requested for approval of subject cited proposed Clinical Trial. Application is on prescribed Form-II, along with prescribed processing fee of Rs. **245,000/-** deposited vide challan no. **972948590**, dated **19-APR-2025**.

2. This clinical trial will be conducted only in Pakistan at Al- Shifa Research Centre, Al-Shifa Trust Eye Hospital, Jhelum Road, Rawalpindi. The site is experienced in conducted multiple global phase II, III studies and is registered with DRAP under license number CTS-0044.

3. The details regarding trial, sponsor and responsible party is as under:

i. **Sponsor: Sinovac (Chengdu) Biotech Co., Ltd**

ii. **Collaborators: DRK Pharma Solutions, Address, 1st Floor, Building No. 1, The Enterprise 15 km, Multan Road, Lahore 53800, Pakistan**

iii. **Purpose of trial: The purpose of this clinical trial is to evaluate the immunogenicity and safety of the serum-free Vero cell-based rabies vaccine developed by Sinovac (Chengdu) Biotech Co., Ltd. in a post-exposure prophylaxis (PEP) schedule. The trial aims to confirm that the vaccine induces a non-inferior immune response compared to the WHO-prequalified Verorab® vaccine and demonstrates a favorable safety profile in both pediatric and adult populations**

iv. **Quantity of IPs required along with justification:** Following are the quantities that are required for 390 participants in the study with the allowed 5% extra buffer.

IPs	Molecule	Strength	Pack Size	Manufacturer	No. of Patients	Patient Dose	Frequency	TOTAL
Rabies Vaccine (Serum-free Vero Cell), for Human Use, Freeze-dried	Inactivated rabies virus antigen	≥2.5 IU per 1.0 mL dose	01 vial of vaccine powder with 1ml solvent	Sinovac (Chengdu) Biotech Co., Ltd.	260 of 390	1.0 ml	5	1365
Verorab® Vaccine	Inactivated rabies virus antigen	≥2.5 IU per 0.5 ml dose	01 vial of vaccine powder with 0.5 ml solvent	Sanofi Pasteur	130 of 390	0.5 ml	5	685
Packaging site with address: Sinovac (Chengdu) Biotech Co., Ltd. Adress: No.618, Fenghuang Road, Shuangliu District, Chengdu, P.R.China								

v. **Source(s) of IPs and Comparator/Ancillary products:**

- Sinovac (Chengdu) Biotech Co., Ltd. Adress: No.618, Fenghuang Road, Shuangliu District, Chengdu, P.R.China
- Verorab® (Sanofi Pasteur)

vi. Wastage and Damage % (along with its justification):

- Active: 1300 * 05% = 1365; Total Import Quantity: 1300 + 65 = 1365
- Placebo/Comparator: 650 * 05% = 685; Total Import Quantity: 650 + 35 = 685
- Other/Ancillary items to be imported for the trial: No Ancillary items are required for import.

vii. Number of subjects to be recruited:390 Subjects (Globally) and 390 Subjects in Pakistan. (Study is only planned to be conducted in Pakistan

viii. Anticipated cost of the project: 468,000/-USD

ix. Study design and details:

Study type	Randomized, Double-Blind, Active-Controlled, Phase III Clinical Trial
Estimated Enrollment:	390
Allocation:	2 (Trial group) :1 (Control group)
Intervention Model:	Parallel Group design
Masking:	Double Blind
Primary Purpose:	To demonstrate the immunogenicity of Sinovac rabies vaccine is noninferior to the active-controlled rabies vaccine (Verorab®) after postexposure prophylaxis (PEP) vaccination.
Official Title:	Immunogenicity and Safety of a Rabies Vaccine (Serum-free Vero Cell), Freeze-dried in Comparison with Verorab®, in a Simulated Post-exposure Prophylaxis Regimen in Healthy Populations Aged ≥1 years: A Randomized, Double-Blind, Active-controlled Phase III Clinical Trial
Estimated Study Start Date:	24-May-2025
Estimated Primary Completion Date:	11-Mar-2026
Estimated Study Completion Date:	10-May-2026

4. Details regarding applied Clinical Trial Sites comprising of primary and secondary objective(s) of the trial/study

S.No.	Name and Licence No. of Site(s)	Approval/Renewal Status as per DRAP's Record
i.	Al-Shifa Research Center', Al Shifa Trust Eye Hospital Rawalpindi, CTS-0044	Valid till 15-Feb-2027

- Primary Outcome Measures/objective(s):
  i. To demonstrate the immunogenicity of Sinovac rabies vaccine is noninferior to the active-controlled rabies vaccine (Verorab®) after postexposure prophylaxis (PEP) vaccination
- Secondary Outcome Measures(s):
  i. To compare the differences of immunogenicity indicators between Sinovac rabies vaccine and Verorab® after PEP vaccination
  ii. To evaluate the safety of Sinovac rabies vaccine.
- Primary Endpoints:
  i. Proportion of participants achieving a rabies virus neutralizing antibody(RVNA) titer ≥0.5 IU/mL at D14 and D28 after the first-dose vaccination, among susceptible participants (RVNA titer <0.5 IU/mL before vaccination)
- Secondary Endpoints:
  i. The geometric mean concentrations(GMCs) of RVNA titers at D14, D28 and D42 after the first-dose vaccination
  ii. Proportion of participants achieving an RVNA titer ≥0.5 IU/mL at D14, D28 and D42 after the first-dose vaccination
  iii. Incidence of adverse reactions within 7 days after each-dose vaccination (If the vaccination interval is less than 7 days, the actual interval shall prevail)

iv. Incidence of adverse reactions from the first dose to 28 days after the last-dose vaccination
v. Incidence of serious adverse events(SAE) from the first dose to 28 days after the last-dose vaccination

5. The details of the submitted documents are as under:

S. No.	Document	Remarks
1	Application on prescribed Form-II	Application submitted on 21-APR-2025 on Form II
2	Prescribed Fee	Prescribed Fee submitted on 19-Apr-2025 challan number 972948590. Attachment available.
3	Investigator Brochure (s)	Investigator's Brochure of Rabies Vaccine (Serum-free Vero Cell) for Human Use, Freeze-dried version 4.0 Dated 15-Dec-2024. Attachment available
4	Final protocol	PRO-PVRV-sf-3002 Protocol of Phase III Clinical Trial (IM PEP) Version 1.0 Dated 08-Jan-2025. Attachment available
5	Informed consent and participant information sheet (Urdu to English)	PRO PRO-PVRV-sf-3002 ICF (≥18 years old and legal guardians) Eng and Urdu Version 1.0 Dated 08-Jan-2025 PRO-PVRV-sf-3002 ICF (8~17years old) Eng and Urdu Version 1.0 Dated 08-Jan-2025 PRO-PVRV-sf-3002 ICF (Pregnant Partner) Eng and Urdu Version 1.0 Dated 08-Jan-2025 Attachment available.
6	List of participating countries	Pakistan. The study is only planned to be conducted in Pakistan.
7	Phase of trial.	Phase III
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import and Export) Rules, 1976 and application for import of trial material.	**<Mention following details>** **Wastage and Damage % will be XX%:** • Active: Active: 1300 * 05% = 1365; Total Import Quantity: 1300 + 65 = 1365 **Freeze-dried powder for solution for injection** • Placebo/Comparator: 650 * 05% = 685; Total Import Quantity: 650 + 35 = 685 Freeze-**dried powder for solution for injection**
9	Site of the trial	Al-Shifa Research Center', Al Shifa Trust Eye Hospital Rawalpindi, CTS-0044 (Study is planned to be conducted at only one site).
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	i. The IRB Approved the clinical trial on 27 Feb 2025 Member included • Prof. Dr. Wajid Ali Khan (Dean Pakistan Institute of Ophthalmology Chief Medical Services Chairman ERC) • Prof. Dr. Nadeem Qureshi (HOD Reina and Chief Consultant) • Prof. Dr. Farah Akhtar (HOD Glaucoma) • Prof. Dr Sumaira Altaf (HOD Pediatric and Strabismus) • Advocate Muhammad Umair (Advocate High court) • Hafiz Main Muhammad (Religious Teacher) • Dr. Muhammad Imran (Consultant General and Laparoscopic Surgeon. Approval letter and IRB Composition attached.

11	Approval of National Bio-ethics Committee (NBC)	The NBC submission is done on the 20th of March 2025. Attachment available.
12	CV's of the Investigators	CV and qualification documents are attached of following: i. Dr. Ume Sughra (PI) ii. Dr. Marriam Suleman (Co-PI)
13	GMP certificate along with COPP and free sale certificate of the investigational product.	• Sinovac (Chengdu) Biotech Co., Ltd. has provided a formal letter confirming compliance with Good Manufacturing Practices (GMP). The Sinovac rabies vaccine is currently under pre-approval review by the National Medical Products Administration (NMPA), China. Attachment available. • Sinovac (Chengdu) Biotech Co., Ltd. Adress: No.618, Fenghuang Road, Shuangliu District, Chengdu, P.R.China • Verorab® Manufactred by Sanofi Pasteur (comparator). Approved by WHO.
14	Pre-clinical/clinical safety studies	The clinical study showed that the immunogenicity of this vaccine was non-inferior to that of the 5-dose licensed control vaccine, whether it was given according to the PEP schedules of Essen (D0, 3, 7, 14, 28) and ACIP four-doses (D0, 3, 7, 14~28). The seropositive rate of the product was 100% at 3 months after the full course of vaccination, and the seropositive rate remained above 97.5% at 6 months after full course. The results of immunogenicity support the recommendations of WHO and national health department on the non-vaccination of re-exposed persons within 3 months after full course. Attachments are available for pre-clinical and clinical safety studies.
15	Summary of Protocol	PRO-PVRV-sf-3002 Summary of Phase III Clinical Trial (IM PEP) Version 1.0 Date 08-Jan-2025 Attachment available.
16	Summary of Investigator Brochure	Summary of Investigator's Brochure_Rabies Vaccine (Serum-free Vero Cell) Version 4.0 Dated 15 Dec 2024 Attachment available.
17	Adverse Event Reporting Form	SAE form attachment available.
18	No of patients to be enrolled in each center.	i. 390 Subjects will be enrolled at Al Shifa Research Center Site. 260 will be in the trial group and 130 will be in the control group 1-9 year = 90 10-17 year = 90 18-59 year = 150 MT 60 year = 60 Total 390 subjects to be enrolled in Pakistan. Total 390 Subjects to be enrolled globally. (study will only be conducted in Pakistan)
19	Name of Monitors and Clinical Research Associate	DRK Pharma Solutions Mobeen Amjad Aaqib Nawaz
20	Evidence of registration in country of origin.	Administrative Document of the National Medical Products Administration. Attachment available.

21	Copy of registration letter (if registered in Pakistan)	Not Applicable (Not Registered in Pakistan)
22	Sample of label of the investigational product / drug.	Primary Label and secondary label for export are available along with the label to be used for blinding.
22	Duration of trial	1 year
23	Undertaking on Stamp paper	Undertaking submitted by Dr. Ume Sughra Principal Investigator of the clinical study Dated 16-Apr-2025

6. In addition to the documents listed in the checklist, the patient-facing documents have also been submitted. These include the following:

i. Diary Card for first vaccination Version 1.0 dated 08-Jan-2025 Eng and urdu
ii. Diary Card for second vaccination Version 1.0 dated 08-Jan-2025 Eng and urdu
iii. Diary Card for Third vaccination Version 1.0 dated 08-Jan-2025 Eng and urdu
iv. Diary Card for Fourth vaccination Version 1.0 dated 08-Jan-2025 Eng and urdu
v. Diary Card for Fifth vaccination Version 1.0 dated 08-Jan-2025 Eng and urdu
vi. Participant Card Version 1.0 dated 23-Jan-2025 Eng and Urdu
vii. Trial Advertisement Version 1.0 dated 30-Jan-2025 Eng and Urdu

7. Evaluator/Assessor remarks:

Based on a complete evaluation of the submitted clinical and nonclinical data, including:

- The Investigator's Brochure and Summary
- The Protocol of the Phase III clinical trial (PRO-PVRV-sf-3002)

Product: Rabies Vaccine (Serum-Free Vero Cell), Freeze-dried
Sponsor: Sinovac (Chengdu) Biotech Co., Ltd.
Trial Phase Reviewed: Phase III (Pakistan, 2025); Previous Phase III (China, 2021–2022)
Primary Indication: Post-exposure prophylaxis (PEP)
Vaccine Type: Inactivated, purified Vero cell rabies vaccine; serum-free, animal-origin-free

8. Following are the shortcomings need to be addressed by the applicant:

A. The product has undergone **only a single Phase III clinical trial** involving 2040 participants aged 10–60. There is no Phase I or II data available to demonstrate. Applicant is requested to justify/address:
   i. omission of Phase I and Phase II trials or provide Phase I or II data available to demonstrate:
      a) First-in-human safety
      b) Initial dose tolerance
      c) Early immunogenicity trends
   ii. was the rabies strain, cell substrate, and manufacturing process previously used in a licensed product?
   iii. Can the sponsor provide bridging data or prior clinical trial references?
   iv. Platform equivalency or submit historical human safety data (e.g., from China's NMPA or other authorities).
   v. Provide rationale for generalizing Phase III results to broader populations (esp. pediatric and elderly) without early safety trials.
   vi. Prior licensed Vero cell rabies vaccine by same sponsor?
   vii. Platform equivalency (same strain, process)? Not explicitly justified
   viii. Extrapolation from other licensed products? Not documented

B. With respect to selection of Excipients
   i. Are all excipients listed in pharmacopoeias or justified by literature?
   ii. Are concentrations within acceptable safety and efficacy ranges?

C. With respect to Compatibility and Interaction Studies:
   i. Drug–excipient and excipient–excipient compatibility data
   ii. Use of stress studies (e.g., FTIR, DSC, HPLC) to identify interactions

iii. Justification for buffering agents, stabilizers, preservatives, etc.

D. With respect to Formulation Optimization Process:
   i. Description of the prototype formulations and the rationale for selecting the final version.

E. **With respect to pre-clinical studies**
   i. **GLP compliance certificates (pre-clinical studies)**
   ii. **Species selection rationale**
   iii. **Justification for dose selection**
   iv. **Statistical analysis** and clinical relevance of findings
   v. *Protective Efficacy in Animal Models*

F. Notification of DSMB not provided (including composition and TORs)

G. GMP Certificate of M/s Sinovac (Chengdu) Biotech Co., Ltd.

H. COA of VERORAB® Vaccine

I. GMP Certificate of M/s Sanofi Pasteur

J. Free Sale Certificate/CoPP of VERORAB® Vaccine in country of origin

K. NBC approval for IB, Study Protocol and other study related documents etc.

L. Furthermore, the proposed site for the trial CTS-0044 is associated with an eye hospital having specialty departments for cornea, retina, glaucoma and cataract surgery. Although during the pandemic some Covid-vaccine trials have been conducted. However, rabies is a very high risk condition with nearly 100% mortality rate. Details regarding emergency department, (Dog Bite Clinic), ID Department and wound management etc. have not been presented in the application.

8. The case was placed before the CSC for consideration.

Decision:

The CSC after deliberation decided to defer the case for further deliberation and submission of reply by the PI regarding following shortcomings:

A. **The product has undergone only a single Phase III clinical trial involving 2040 participants aged 10–60. There is no Phase I or II data available to demonstrate. Applicant is required to justify/address:**
   i. **Omission of Phase I and Phase II trials or provide Phase I or II data available to demonstrate:**
      a) **First-in-human safety.**
      b) **Initial dose tolerance.**
      c) **Early immunogenicity trends.**
   ii. **Was the rabies strain, cell substrate, and manufacturing process previously used in a licensed product.**
   iii. **Can the sponsor provide bridging data or prior clinical trial references?**
   iv. **Platform equivalency or submit historical human safety data (e.g., from China's NMPA or other authorities).**
   v. **Provide rationale for generalizing Phase III results to special populations (pediatric and elderly) without early safety trials.**
   vi. **Prior licensed Vero cell rabies vaccine by same sponsor.**
   vii. **Platform equivalency (same strain, process) not explicitly justified.**
   viii. **Extrapolation from other licensed products not documented.**

B. **With respect to selection of Excipients**
   i. **Are all excipients listed in pharmacopoeias or justified by literature.**
   ii. **Are concentrations within acceptable safety and efficacy ranges.**

C. **With respect to Compatibility and Interaction Studies:**
   i. **Drug–excipient and excipient–excipient compatibility data.**
   ii. **Use of stress studies (e.g., FTIR, DSC, HPLC) to identify interactions.**
   iii. **Justification for buffering agents, stabilizers, preservatives, etc.**

D. **With respect to Formulation Optimization Process:**
   i. **Description of the prototype formulations and the rationale for selecting the final version.**

E. **With respect to pre-clinical studies**
   i. **GLP compliance certificates (pre-clinical studies)**
   ii. **Species selection rationale**
   iii. **Justification for dose selection**
   iv. **Statistical analysis and clinical relevance of findings**

v. Protective Efficacy in Animal Models

F. **Notification of DSMB not provided (including composition and TORs)**
G. **GMP Certificate of M/s Sinovac (Chengdu) Biotech Co., Ltd.**
H. **COA of VERORAB® Vaccine**
I. **GMP Certificate of M/s Sanofi Pasteur**
J. **Free Sale Certificate/CoPP of VERORAB® Vaccine in country of origin**
K. **NBC approval for IB, Study Protocol and other study related documents etc.**
L. **Details regarding emergency department, (Dog Bite Clinic), ID Department and wound management etc. have not been presented in the application.**

CASE No. 3.10:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED, "IMMUNOGENICITY AND SAFETY OF A RABIES VACCINE (SERUM-FREE VERO CELL), FREEZE-DRIED IN COMPARISON WITH VERORAB®, IN A SIMULATED PRE-EXPOSURE PROPHYLAXIS REGIMEN IN HEALTHY POPULATIONS AGED ≥1 YEARS: A RANDOMIZED, DOUBLE-BLIND, ACTIVE-CONTROLLED PHASE III CLINICAL TRIAL. NO. F. 03-71/2025-CT(PS)

Application No. nil dated 21-04-2025 from Dr. Ume Sughra, Principal Investigator and Al-Shifa Trust Eye Hospital, Jhelum Road, Rawalpindi regarding subject cited above, wherein request they have requested for approval of subject cited proposed Clinical Trial. Application is on prescribed Form-II, along with prescribed processing fee of Rs. 245,000/- deposited vide challan no. 87734612, dated 19-APR-2025.

2. This clinical trial will be conducted only in Pakistan at Al- Shifa Research Centre, Al-Shifa Trust Eye Hospital, Jhelum Road, Rawalpindi. The site is experienced in conducted multiple global phase II, III studies and is registered with DRAP under license number CTS-0044.

3. The details regarding trial, sponsor and responsible party is as under:

i. **Sponsor: Sinovac (Chengdu) Biotech Co., Ltd**

ii. **Collaborators: DRK Pharma Solutions, Address, 1st Floor, Building No. 1, The Enterprise 15 km, Multan Road, Lahore 53800, Pakistan**

iii. **Purpose of trial: The purpose of this clinical trial is to evaluate the immunogenicity and safety of the serum-free Vero cell-based rabies vaccine developed by Sinovac (Chengdu) Biotech Co., Ltd. in a post-exposure prophylaxis (PEP) schedule. The trial aims to confirm that the vaccine induces a non-inferior immune response compared to the WHO-prequalified Verorab® vaccine and demonstrates a favorable safety profile in both pediatric and adult populations**

iv. **Quantity of IPs required along with justification:** Following are the quantities that are required for 390 participants in the study with the allowed 5% extra buffer.

IPs	Molecule	Strength	Pack Size	Manufacturer	No. of Patients	Patient Dose	Frequency	TOTAL
Rabies Vaccine (Serum-free Vero Cell), for	Inactivated rabies virus antigen	≥2.5 IU per 1.0 mL dose	01 vial of vaccine powder with 1 ml	Sinovac (Chengdu) Biotech Co.,	260 of 390	1.0 ml	3	819

human use, Freeze-dried			**solvent**	**Ltd.**				
Verorab® vaccine	**Inactivated rabies virus antigen**	≥2.5 IU per 0.5 ml dose	**01 vial of vaccine powder with 0.5 ml solvent**	Sanofi Pasteur	130 of 390	0.5 ml	3	410
Packaging site with address: Sinovac (Chengdu) Biotech Co., Ltd. Adress: No.618, Fenghuang Road, Shuangliu District, Chengdu, P.R.China								

v. **Source(s) of IPs and Comparator/Ancillary products:**
- Sinovac (Chengdu) Biotech Co., Ltd. Adress: No.618, Fenghuang Road, Shuangliu District, Chengdu, P.R.China
- Verorab® (Sanofi Pasteur)

vi. **Wastage and Damage % (along with its justification):**
- Active: 780 * 05% = 819; Total Import Quantity: 780 + 39 = 819
- Placebo/Comparator: 390 * 05% = 410 ; Total Import Quantity: 390 + 20 = 410
- Other/Ancillary items to be imported for the trial: No Ancillary items are required for import.

vii. **Number of subjects to be recruited:** 390 Subjects (Globally) and 390 Subjects in Pakistan. (Study is only planned to be conducted in Pakistan

viii. **Anticipated cost of the project:** 390,000/-USD

ix. **Study design and details:**

Study type	Randomized, Double-Blind, Active-Controlled, Phase III Clinical Trial
Estimated Enrollment:	390
Allocation:	2 (Trial group) :1 (Control group)
Intervention Model:	Parallel Group design
Masking:	Double Blind
Primary Purpose:	To demonstrate the immunogenicity of Sinovac rabies vaccine is noninferior to the active-controlled rabies vaccine (Verorab®) after a three-dose pre-exposure prophylaxis (PrEP) vaccination at D0, 7, 28. To demonstrate the immunogenicity of Sinovac rabies vaccine is noninferior to Verorab® after a two-dose PrEP vaccination at D0, 7.
Official Title:	Immunogenicity and Safety of a Rabies Vaccine (Serum-free Vero Cell), Freeze-dried in Comparison with Verorab®, in a Pre-exposure Prophylaxis Regimen in Healthy Populations Aged ≥1 years: A Randomized, Double-Blind, Active controlled Phase III Clinical Trial
Estimated Study Start Date:	24-May-2025
Estimated Primary Completion Date:	11-Mar-2026
Estimated Study Completion Date:	10-May-2026

4. Details regarding applied Clinical Trial Sites comprising of primary and secondary objective(s) of the trial/study

S.No.	Name and Licence No. of Site(s)	Approval/Renewal Status as per DRAP's Record
i.	Al-Shifa Research Center', Al Shifa Trust Eye Hospital Rawalpindi, CTS-0044	Valid till 15-Feb-2027

- Primary Outcome Measures/objective(s):

i. To demonstrate the immunogenicity of Sinovac rabies vaccine is noninferior to the active-controlled rabies vaccine (Verorab®) after a three-dose pre-exposure prophylaxis (PrEP) vaccination at D0, 7, 28

ii. To demonstrate the immunogenicity of Sinovac rabies vaccine is noninferior to Verorab® after a two-dose PrEP vaccination at D0, D7

- Secondary Outcome Measures(s):
  i. To compare the differences of immunogenicity indicators between Sinovac rabies vaccine and Verorab® after PrEP vaccination
  ii. To evaluate the safety of Sinovac rabies vaccine.
- Primary Endpoints:
  ii. Proportion of participants achieving a rabies virus neutralizing antibody (RVNA) titer ≥0.5 IU/mL at D42 after the first-dose vaccination, among susceptible participants (RVNA titer <0.5 IU/mL before vaccination)
  iii. Proportion of participants achieving an RVNA titer ≥0.5 IU/mL at D28 after the first-dose vaccination, among susceptible participants (RVNA titer <0.5 IU/mL before vaccination)
- Secondary Endpoints:
  vi. The geometric mean concentrations(GMCs) of RVNA titers at D28 and D42 after the first-dose vaccination
  vii. Proportion of participants achieving an RVNA titer ≥0.5 IU/mL at D28 and D42 after the first-dose vaccination
  viii. Incidence of adverse reactions within 7 days after each-dose vaccination (If the vaccination interval is less than 7 days, the actual interval shall prevail)
  ix. Incidence of adverse reactions from the first dose to 28 days after the last-dose vaccination
  x. Incidence of serious adverse events(SAE) from the first dose to 28 days after the last-dose vaccination

5. The details of the submitted documents are as under:

S. No.	Document	Remarks
1	Application on prescribed Form-II	Application submitted on 21-APR-2025 on Form II
2	Prescribed Fee	Prescribed Fee submitted on 19-Apr-2025 challan number 87734612. Attachment available.
3	Investigator Brochure (s)	Investigator's Brochure of Rabies Vaccine (Serum-free Vero Cell) for Human Use, Freeze-dried version 4.0 Dated 15-Dec-2024. Attachment available
4	Final protocol	PRO-PVRV-sf-3003 Protocol of Phase III Clinical Trial (IM PrEP) Version 1.0 Dated 08-Jan-2025. Attachment available
5	Informed consent and participant information sheet (Urdu to English)	PRO PRO-PVRV-sf-3003 ICF (≥18 years old and legal guardians) Eng and Urdu Version 1.0 Dated 08-Jan-2025 PRO-PVRV-sf-3003 ICF (8~17years old) Eng and Urdu Version 1.0 Dated 08-Jan-2025 PRO-PVRV-sf-3003 ICF (Pregnant Partner) Eng and Urdu Version 1.0 Dated 08-Jan-2025 Attachment available.
6	List of participating countries	Pakistan. The study is only planned to be conducted in Pakistan.
7	Phase of trial.	Phase III
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import and Export) Rules,	**Wastage and Damage % will be XX%:** • Active: Active: 780 * 05% = 819; Total Import Quantity: 780 + 39 = 819 **Freeze-dried powder for solution for injection** • Placebo/Comparator: 390 * 05% = 410 ; Total

	1976 and application for import of trial material.	Import Quantity: 390 + 20 = 410 **Freeze-dried powder for solution for injection**
9	Site of the trial	Al-Shifa Research Center', Al Shifa Trust Eye Hospital Rawalpindi, CTS-0044 (Study is planned to be conducted at only one site).
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	i. The IRB Approved the clinical trial on 27 Feb 2025 Member included • Prof. Dr. Wajid Ali Khan (Dean Pakistan Institute of Ophthalmology Chief Medical Services Chairman ERC) • Prof. Dr. Nadeem Qureshi (HOD Reina and Chief Consultant) • Prof. Dr. Farah Akhtar (HOD Glaucoma) • Prof. Dr Sumaira Altaf (HOD Pediatric and Strabismus) • Advocate Muhammad Umair (Advocate High court) • Hafiz Main Muhammad (Religious Teacher) • Dr. Muhammad Imran (Consultant General and Laparoscopic Surgeon. Approval letter and IRB Composition attached.
11	Approval of National Bio-ethics Committee (NBC)	The NBC submission is done on the 20th of March 2025. Attachment available.
12	CV's of the Investigators	CV and qualification documents are attached of following: iii. Dr. Ume Sughra (PI) iv. Dr. Marriam Suleman (Co-PI)
13	GMP certificate along with COPP and free sale certificate of the investigational product.	• Sinovac (Chengdu) Biotech Co., Ltd. has provided a formal letter confirming compliance with Good Manufacturing Practices (GMP). The Sinovac rabies vaccine is currently under pre-approval review by the National Medical Products Administration (NMPA), China. Attachment available. • Sinovac (Chengdu) Biotech Co., Ltd. Adress: No.618, Fenghuang Road, Shuangliu District, Chengdu, P.R.China • Verorab® Manufactred by Sanofi Pasteur (comparator). Approved by WHO.

14	Pre-clinical/clinical safety studies	The clinical study showed that the immunogenicity of this vaccine was non-inferior to that of the 5-dose licensed control vaccine, whether it was given according to the PEP schedules of Essen (D0, 3, 7, 14, 28) and ACIP four-doses (D0, 3, 7, 14~28). The seropositive rate of the product was 100% at 3 months after the full course of vaccination, and the seropositive rate remained above 97.5% at 6 months after full course. The results of immunogenicity support the recommendations of WHO and national health department on the non-vaccination of re-exposed persons within 3 months after full course. Attachments are available for pre-clinical and clinical safety studies.
15	Summary of Protocol	PRO-PVRV-sf-3003 Summary of Phase III Clinical Trial (IM PrEP) Version 1.0 Date 08-Jan-2025 Attachment available
16	Summary of Investigator Brochure	Summary of Investigator's Brochure_Rabies Vaccine (Serum-free Vero Cell) Version 4.0 Dated 15 Dec 2024 Attachment available
17	Adverse Event Reporting Form	SAE form attachment available.
18	No of patients to be enrolled in each center.	ii. 390 Subjects will be enrolled at Al Shifa Research Center Site. 260 will be in the trial group and 130 will be in the control group 1-9 year = 90 10-17 year = 90 18-59 year = 150 MT 60 year = 60 Total 390 subjects to be enrolled in Pakistan. Total 390 Subjects to be enrolled globally. (study will only be conducted in Pakistan)
19	Name of Monitors and Clinical Research Associate	DRK Pharma Solutions Mobeen Amjad Aaqib Nawaz
20	Evidence of registration in country of origin.	Administrative Document of the National Medical Products Administration. Attachment available.
21	Copy of registration letter (if registered in Pakistan)	Not Applicable (Not Registered in Pakistan)
22	Sample of label of the investigational product / drug	Primary Label and secondary label for export are available along with the label to be used for blinding.
22	Duration of trial	1 year

23	Undertaking on Stamp paper	Undertaking submitted by Dr. Ume Sughra Principal Investigator of the clinical study Dated 16-Apr-2025

6. In addition to the documents listed in the checklist, the patient-facing documents have also been submitted. These include the following:

i. Diary Card for first vaccination version 1.0 Dated 08-Jan-2025 Eng and urdu
ii. Diary Card for second vaccination version 1.0 Dated 08-Jan-2025 Eng and urdu
iii. Diary Card for Third vaccination version 1.0 Dated 08-Jan-2025 Eng and urdu
iv. Participant Card Version 1.0 Dated 23-Jan-2025 Eng and Urdu
v. Trial Advertisement Version 1.0 Dated 30-Jan-2025 Eng and Urdu

7. Evaluator/Assessor remarks:

Based on a complete evaluation of the submitted clinical and nonclinical data, including:

- The Investigator's Brochure and Summary
- The Protocol of the Phase III clinical trial (PRO-PVRV-sf-3003)

Product: Rabies Vaccine (Serum-Free Vero Cell), Freeze-dried
Sponsor: Sinovac (Chengdu) Biotech Co., Ltd.
Trial Phase Reviewed: Phase III (Pakistan, 2025); Previous Phase III (China, 2021–2022)
Primary Indication: Pre-exposure prophylaxis (PrEP)
Vaccine Type: Inactivated, purified Vero cell rabies vaccine; serum-free, animal-origin-free

8. Following are the shortcomings need to be addressed by the applicant:

M. The product has undergone **only a single Phase III clinical trial** involving 2040 participants aged 10–60. There is no Phase I or II data available to demonstrate. Applicant is requested to justify/address:
   i. omission of Phase I and Phase II trials or provide Phase I or II data available to demonstrate:
      d) First-in-human safety
      e) Initial dose tolerance
      f) Early immunogenicity trends
   ii. was the rabies strain, cell substrate, and manufacturing process previously used in a licensed product?
   iii. Can the sponsor provide bridging data or prior clinical trial references?
   iv. Platform equivalency or submit historical human safety data (e.g., from China's NMPA or other authorities).
   v. Provide rationale for generalizing Phase III results to broader populations (esp. pediatric and elderly) without early safety trials.
   vi. Prior licensed Vero cell rabies vaccine by same sponsor?
   vii. Platform equivalency (same strain, process)? Not explicitly justified
   viii. Extrapolation from other licensed products? Not documented

N. With respect to selection of Excipients
   iii. Are all excipients listed in pharmacopoeias or justified by literature?
   iv. Are concentrations within acceptable safety and efficacy ranges?

O. With respect to Compatibility and Interaction Studies:
   iv. Drug–excipient and excipient–excipient compatibility data
   v. Use of stress studies (e.g., FTIR, DSC, HPLC) to identify interactions
   vi. Justification for buffering agents, stabilizers, preservatives, etc.

P. With respect to Formulation Optimization Process:
   ii. Description of the prototype formulations and the rationale for selecting the final version.

Q. **With respect to pre-clinical studies**
   vi. **GLP compliance certificates (pre-clinical studies)**
   vii. **Species selection rationale**
   viii. **Justification for dose selection**
   ix. **Statistical analysis** and clinical relevance of findings

x. *Protective Efficacy in Animal Models*

R. Notification of DSMB not provided (including composition and TORs)
S. GMP Certificate of M/s Sinovac (Chengdu) Biotech Co., Ltd.
T. COA of VERORAB® Vaccine
U. GMP Certificate of M/s Sanofi Pasteur
V. Free Sale Certificate/CoPP of VERORAB® Vaccine in country of origin
W. NBC approval for IB, Study Protocol and other study related documents etc.
X. Furthermore, the proposed site for the trial CTS-0044 is associated with an eye hospital having specialty departments for cornea, retina, glaucoma and cataract surgery. Although during the pandemic some Covid-vaccine trials have been conducted. However, rabies is a very high risk condition with nearly 100% mortality rate. Details regarding emergency department, (Dog Bite Clinic), ID Department and wound management etc. have not been presented in the application.

8. The case was placed before the CSC for consideration.

Decision:

The CSC after deliberation decided to defer the case for further deliberation and submission of reply by the PI regarding following shortcomings:

A. The product has undergone only a single Phase III clinical trial involving 2040 participants aged 10–60. There is no Phase I or II data available to demonstrate. Applicant is required to justify/address:
  - **i. Omission of Phase I and Phase II trials or provide Phase I or II data available to demonstrate:**
    - **a) First-in-human safety.**
    - **b) Initial dose tolerance.**
    - **c) Early immunogenicity trends.**
  - **ii. Was the rabies strain, cell substrate, and manufacturing process previously used in a licensed product.**
  - **iii. Can the sponsor provide bridging data or prior clinical trial references.**
  - **iv. Platform equivalency or submit historical human safety data (e.g., from China's NMPA or other authorities).**
  - **v. Provide rationale for generalizing Phase III results to special populations (pediatric and elderly) without early safety trials.**
  - **vi. Prior licensed Vero cell rabies vaccine by same sponsor.**
  - **vii. Platform equivalency (same strain, process) not explicitly justified**
  - **viii. Extrapolation from other licensed products not documented**

B. With respect to selection of Excipients
  - **i. Are all excipients listed in pharmacopoeias or justified by literature.**
  - **ii. Are concentrations within acceptable safety and efficacy ranges.**

C. With respect to Compatibility and Interaction Studies:
  - **i. Drug–excipient and excipient–excipient compatibility data.**
  - **ii. Use of stress studies (e.g., FTIR, DSC, HPLC) to identify interactions.**
  - **iii. Justification for buffering agents, stabilizers, preservatives, etc.**

D. With respect to Formulation Optimization Process:
  - **i. Description of the prototype formulations and the rationale for selecting the final version.**

E. With respect to pre-clinical studies
  - **i. GLP compliance certificates (pre-clinical studies).**
  - **ii. Species selection rationale.**
  - **iii. Justification for dose selection.**
  - **iv. Statistical analysis and clinical relevance of findings.**
  - **v. Protective Efficacy in Animal Models.**

F. Notification of DSMB not provided (including composition and TORs).
G. GMP Certificate of M/s Sinovac (Chengdu) Biotech Co., Ltd.
H. COA of VERORAB® Vaccine.
I. GMP Certificate of M/s Sanofi Pasteur.
J. Free Sale Certificate/CoPP of VERORAB® Vaccine in country of origin.
K. NBC approval for IB, Study Protocol and other study related documents etc.

L. **Details regarding emergency department, (Dog Bite Clinic), ID Department and wound management etc. have not been presented in the application.**

CASE No. 3.11:

APPLICATION FOR APPROVAL AND REGISTRATION OF PHASE III CLINICAL TRIAL TITLED, "MULTI-CENTER. RANDOMIZED, DOUBLE BLIND AND PLACEBO CONTROLLED CLINICAL TRIAL ON THE AND SAFETY OF JINIIUA QINGGAN (JHQG) GRANULES FOR THE TREATMENT OF ACUTE UPPER RESPIRATORY INFECTION (WIND-HEAT PATTERN). F. No.03-72/2025-CT (PS)

Application for approval of subject Clinical Trial was received from Dr. Muhammad Raza Shah, Director, CBSCR, International Center for Chemical & Biological Sciences, University of Karachi, dated 14th May 2025. Wherein request has been made for registration & approval of subject Clinical Trial. Application is on prescribed Form-II, with prescribed processing fee of Rs. 245,000 paid vide challan No. 30908938, dated 12th May 2025.

2. The case was placed before the CSC for consideration.

Decision:

The CSC decided to defer the case for further deliberation.

CASE No. 3.12:

APPLICATION FOR APPROVAL AND REGISTRATION OF PHASE III CLINICAL TRIAL TITLED, "RANDOMIZED TRIAL TO EVALUATE AND COMPARE THE IMMUNOGENICITY AND SAFETY OF HEXAVALENT VACCINE IN HEALTHY INFANTS IN A POLIO-ENDEMIC COUNTRY". F. No.03-73/2025-CT (PS)

Application for approval of subject Clinical Trial was received from Dr. Ali Faisal Saleem, Aga Khan University Hospital, Karachi, dated 28th April 2025. Wherein request has been made for registration & approval of subject Clinical Trial. Application is on prescribed Form-II, with prescribed processing fee of Rs. 245,000 paid vide challan No. 5891280810.

2. The case was placed before the CSC for consideration.

Decision:

The CSC decided to defer the case for further deliberation.

AGENDA ITEM 4: AMENDMENTS

CASE No. 4.1:

APPLICATION FOR AMENDMENT IN ALREADY APPROVED BIOEQUIVALENCE STUDY OF PERISPA (EPERISONE) 50 MG TABLETS MANUFACTURED BY M/S PLATINUM PHARMACEUTICALS (PVT) LIMITED, KARACHI. COMPARED WITH MYONAL (EPERISONE) 50MG TABLETS MANUFACTURED BY M/S EISAI Co. LTD., JAPAN. F. No. 14-02/2022-BA/BE-S (PS)

An application was forwarded by Dr. Badar Uddin Ujjan (PI of the BA/BE Study), Institute of Biological & Pharmaceutical Sciences (IBBPS), Dow University of Health Sciences, Ojha

Campus Karachi, dated 22nd April, 2025. Wherein, application is amendment in already approved BA/BE Study.

2. It is submitted that the application was discussed in 47th CSC meeting dated 22nd December 2023, and the CSC decided the case as follows:

The CSC after detailed deliberation, decided the case as follows:

a. *to approve the BA/BE Study titled, "Bioequivalence Study of Perispa (Eperisone HCI) Tablet 50mg, a single-dose, randomized, open-label, two-period, two-sequence, two treatments, 2 x 2, crossover bioequivalence study of Perispa (Eperisone HCL) Tablet 50mg compared with Myonal (Eperisone HCL) Tablet 50mg in 34 healthy adult human subjects, under fasting condition." to be conducted at IBBPS-DUHS, Ojha Campus, SUPARCO Road, Karachi.*
b. *PI will provide details of reference product regarding Import license, mode of purchase, shipment details for record.*

3. Accordingly, after finalization of the minutes of the meeting, the decision letter was communicated vide letter bearing number F.No.16-47/2023-CSC dated 08th January 2024 and after approval registration letter of the subject BA/BE Study was issued on 11th January 2024.

4. The study (protocol version 2.0, dated 3rd July 2023) was approved for 34 subjects and for a maximum study duration of 15±4 days. The PI was further directed for submission of details regarding the reference product and documents (e.g. Country of origin, mode of purchase, shipment procedure, Import license) along with any other relevant documents.

5. PI hasn't provided any details regarding IMPs (e.g. Country of origin, mode of purchase, shipment procedure, Import license) and failed to conduct study within the stipulated time.

6. Application is reproduced as under:

Ref, no. DUHS/IBBPS/R/2025/04-147 *Date: April 22, 2025*

To,

The Deputy Director
Clinical Studies Committee,
Drug Regulatory Authority Pakistan
Islamabad

Subject: Protocol Amendment version 3.0 for DRAP Approved Bioequivalence Study of Perispa (Eperisone HCL) Tablet 50mg (Ref: F. No. 14-02/2022- BA/BE-S (PS)

Respected Sir/Madam,

Reference to subject, we M/s Institute of Biological, Biochemical & Pharmaceutical Sciences, DUHS, hereby submitting Protocol amendment version 3.0 for DRAP approved Bioequivalence Study of Perispa (Eperisone HCI) Tablet 50mg Ref: F. No. 14-02/2022-BA/BE-S (PS) for your reference & record.

Study Title: An open-label, single-dose, fully replicated, two-sequence, four-period, two-treatment crossover bioequivalence study of Perispa (Eperisone HCL) Tablet 50mg.

Enclosed please find the following:

1) *A copy of Change history.*
2) *A copy of Amended Protocol version 3.0*
3) *A copy of Case Report Form.*
4) *A copy of Medical Screening Form.*

5) *A copy of Informed Consent Form (Both Urdu & English)*
6) *A copy of Revised Sponsor CRO agreement.*

7. Change history of amended protocol version 3.0 is as follows:

S.No.	*SECTION*	*DESCRIPTION OF CHANGE*	*BRIEF RATIONALE*
01	*Page 1*	***Change of Protocol Version:*** *The version was previously Version 2.0 which is now changed to Version 3.0*	*To demonstrate the bioequivalence of a highly variable drug, a fully replicated, two-sequence, four-period, two-treatment crossover bioequivalence study is required.*
02	*1. Protocol Summary 2. Design (15.1)*	***Study Title:*** *The study title was updated to replace the "randomized, two-period, 2x2 crossover" with "fully replicated, two-sequence, four-period, two-treatment crossover" to reflect the revised study design accurately.*	*The study design is revised to a fully replicated, two-sequence, four-period crossover to assess within-subject variability and apply reference scaled average bioequivalence (RSABE), which is recommended for highly variable drugs (HVDs) in the FDA (2013) and EMA (2010) bioequivalence guidelines.*
03	*1. Protocol Summary 2. Blood Sampling Time Points, Total Blood Volume (25.2)*	***Blood Sampling Time Points, Total Blood Volume, and Handling:*** *Addition of post-dose 14th hr. time point in the sampling schedule. In this study, 16 ml of blood will be collected during screening, 52 ml during each period, and 8 ml for study follow-up from each subject. Therefore, a total of232 ml blood volume will be collected from each subject during the whole study, which is less than the amount of blood donated in one voluntary blood donation.*	*The blood sampling time points are revised to ensure adequate characterization of the pharmacokinetic (PK) profile of Eperisone HCl, with sufficient sampling around Cmax, elimination phase, and half-life (t½).*
04	*18. Handling, Storage, Accountability, Dispensing & Retention Procedures for Investigational Medicinal Products*	***Handling, Storage, Accountability, Dispensing & Retention Procedures for Investigational Medicinal Products:*** *18.5: The personnel responsible should be stated as QA personnel, Investigator, or Medical Officer (MO).*	*Adding a Medical Officer (MO) for Investigational Product (IP) administration ensures patient safety through immediate medical supervision and emergency management during dosing. It fulfills GCP and regulatory requirements for physician oversight, improves the accuracy of documentation, and enables real-time observation.*
05	*19.3 Laboratory Tests Page 26*	***Laboratory Tests:*** *Serology The HAV Total test removed from screening. Hepatitis A antibody IGM will suffice the need of screening.*	*Since HA V IgM is already included and is more relevant for detecting acute infection.*
06	*1.Protocol Summary*	***Restrictions:*** *Alcohol Test to be conducted using breath sample instead of urine.*	*Breath alcohol testing provides immediate, non-invasive, and reliable results, reflecting the current blood alcohol concentration (BAC) at the time of testing. It is quicker and more practical than urine testing, which may not accurately represent real-time alcohol levels and can detect alcohol consumed hours earlier.*

07	*1.Protocol Summary*	***Sequence of Investigational drug:*** *Sequence of giving investigational drug has been changed to TRTR and RTRT.*	*The sequence of administering the investigational drug was changed to TRTR and RTRT to align with the requirements of a fully replicated, two-sequence, four-period, two-treatment crossover design. This adjustment ensures that each subject receives both the test (T) and reference (R) products twice, allowing for the calculation of within-subject variability for both treatments.*
08	*1.Protocol Summary*	***Housing:*** *From 12 hours prior to dosing and 14 hours' post-dose in Periods 1, II, III and IV, for a total of at least 26 hours in each period. The total confinement period will be 26 hours instead of 24 hrs. in each period.*	*The addition of 14.00-hour time point is to ensure adequate characterization of the pharmacokinetic (PK) profile of Eperisone HCl, with sufficient sampling around Cmax, elimination phase, and half-life (t½).*
09	*15. Study Design and Rationale*	***Study design, Study rationale:*** *An open-label, single-dose, fully replicated, two-sequence, four-period, two-treatment crossover bioequivalence study of Perispa (Eperisone HCl) Tablet 50mg.*	*The observed intra-subject variability is greater than 50%. Therefore, as per FDA and EMA guidelines, this product falls under the category of a highly variable drug. To demonstrate the bioequivalence of a highly variable drug, a fully replicated, two-sequence, four-period, two-treatment crossover bioequivalence study 1s required.*
10	*1.Protocol Summary*	***Safety monitoring:*** *Removal ofCOVID-19 test because it is not a mandatory requirement now.*	*Routine COVID-19 testing has been removed from safety monitoring due to low disease prevalence in the region.*

8. After initial evaluation following shortcoming and clarifications need to submitted by the PI:

i. Prescribed processing fee for the amendment need to be provided.
ii. IRB/ERC approval for amendments.
iii. NBC approval for amendments.
iv. The study (protocol version 2.0, dated 3rd July 2023) was approved for 34 subjects with maximum study duration of 15±4 days (as applied). Further it was directed to submit details regarding reference product and documents (e.g. Country of origin, mode of purchase, shipment procedure, Import license) along with any other relevant documents, but PI hasn't provided any details regarding IMPs (e.g. Country of origin, mode of purchase, shipment procedure, Import license) and failed to conduct study within the stipulated time, justification in this regard is required.

9. In the view of the above, the shortcomings letter was communicated to the applicant, response yet awaited.

10. The case was placed before the CSC for consideration.

Decision:

The CSC after deliberation deferred the case for the submission of the following:

i. **Prescribed processing fee for the amendment need to be provided.**
ii. **IRB/ERC approval for amendments.**
iii. **NBC approval for amendments.**
iv. **The study (protocol version 2.0, dated 3rd July 2023) was approved for 34 subjects with maximum study duration of 15±4 days (as applied). Further it was directed to submit details regarding reference product and documents (e.g. Country of origin, mode of purchase, shipment procedure, import license) along with any other relevant documents, but PI hasn't provided any details regarding IMPs (e.g. Country of origin, mode of purchase, shipment procedure, import license) and failed to conduct study within the stipulated time, justification in this regard is required.**

CASE No. 4.2:

APLICATION FOR APPROVAL OF PROTOCOL AMMEMDMENT VERSION 5.0 AND ASSOCIATED DOCUMENTS FOR ALREADY APPROVED CLINICAL TITLE "A PHASE II, RANDOMIZED, OBSERVER-BLINDED, PLACEBO CONTROLLED TRIAL TO EVALUATE TIIE SAFETY AND IMMUNOGENICITY OF IIECOLIN ® IN HEALTIIY PREGNANT WOMEN BETWEEN GESTATIONAL AGE 14-34 WEEKS AND NON-PREGNANT WOMEN OF 16-45 YEARS OLD". F.NO.03-35/2023-CT (PS)

Document	Page	Before	After	Rational

Application is received from the PI of the trial Dr. M. Imran Nisar, Principal Investigator, Associate Professor & Vice Chair Research Department of Pediatrics and Child Health, The Aga Khan University, Pakistan vide letter dated 21st April, 2025 wherein a request for approval of protocol amendment and associated documents has been made which is reproduced as under: -

In reference to the clinical trial as stated above, approved under registration number CT-0058, I am writing to request your approval for Protocol Amendment 5.0, dated 21 March 2025, and its associated documents.

This amendment has also been submitted to the Aga Khan University Institutional Ethical Review Committee (ERC/IRB) and the National Bioethics Committee (NBC). The approval from the AKU ERC is attached for your reference, and the approval from NBC will be shared upon availability.

The fee for the protocol amendment (PKR 122,530/-) has been submitted, and the receipt (No. 49758126386) is attached with the application

Below is the list of documents requiring your approval:

SR No.	*Document*	*Effective Version*	*Effective Date*
1	*IVI_Hecolin_P001_Protocol_V5.0_21 MAR2025_*	*Version 5.0*	*21 March 2025*
2	*IVI_Hecolin_P001_CRF_V5.0_Bilingu al_28Mar2025*	*Version 5.0*	*28 March 2025*

For your reference and records, the following documents are also submitted for your consideration:

1. *AKU ERC approval letter (Dated: 16-Apr-2025)*
2. *Summary of Changes*
3. *Fee Receipt*

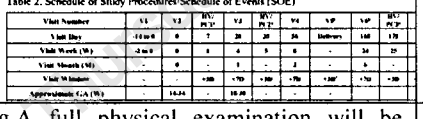
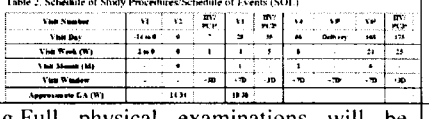
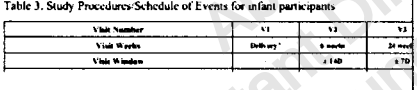
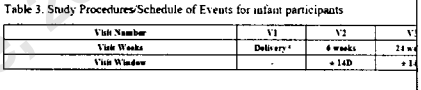
The summary of changes is reproduced as under: -

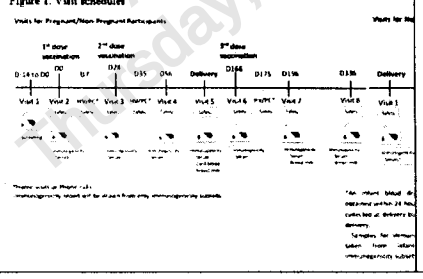
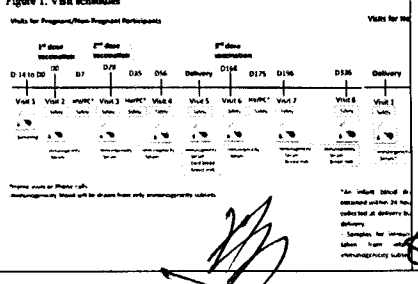
TITLE OF STUDY:	A Phase II, Randomized, Observer-blinded, Placebo Controlled Trial to Evaluate the Safety and Immunogenicity of Hecolin® in Healthy Pregnant Women between Gestational Age 14-34 weeks and Non-Pregnant Women of 16-45 years old		
PROTOCOL NUMBER:	**IVI Hecolin P001**	**VERSION NUMBER/DATE:**	**5.0 / 21Mar2025**

Type (eg. Protocol, ICF)				e for the Change
Protocol	All, Footer	IVI_Hecolin_P001_Protocol_V4.0_25Jun2024	IVI_Hecolin_P001_Protocol_V5.0_21Mar2024	Protocol version and date is updated.
	1	Funding Agency: Open Philanthropy / BMGF / Thrasher Version Number and Date: Version 4.0, 25 Jun 2024 Version History Version Number | Date Version 1.0 | 27 Oct 2022 Version 2.0 | 03 Feb 2023 Version 3.0 | 10 May 2023 Version 4.0 | 25 Jun 2024	Funding Agency: Open Philanthropy / BMGF / Thrasher Version Number and Date: Version 5.0, 21 Mar 2025 Version History Version Number | Date Version 1.0 | 27 Oct 2022 Version 2.0 | 03 Feb 2023 Version 3.0 | 10 May 2023 Version 4.0 | 25 Jun 2024 Version 5.0 | 21 Mar 2025	Protocol version and date is updated.
	2-5	Please refer to the Table of Content in page 2-5	Please refer to the Table of Content in page 2-5	Page numbers are updated
Document Type (eg. Protocol, ICF)	**Page**	**Before**	**After**	**Rationale for the Change**
Protocol	All, Footer	IVI_Hecolin_P001_Protocol_V4.0_25Jun2024	IVI_Hecolin_P001_Protocol_V5.0_21Mar2024	Protocol version and date is updated.
	1	Funding Agency: Open Philanthropy / BMGF / Thrasher Version Number and Date: Version 4.0, 25 Jun 2024 Version History Version Number | Date Version 1.0 | 27 Oct 2022 Version 2.0 | 03 Feb 2023 Version 3.0 | 10 May 2023 Version 4.0 | 25 Jun 2024	Funding Agency: Open Philanthropy / BMGF / Thrasher Version Number and Date: Version 5.0, 21 Mar 2025 Version History Version Number | Date Version 1.0 | 27 Oct 2022 Version 2.0 | 03 Feb 2023 Version 3.0 | 10 May 2023 Version 4.0 | 25 Jun 2024 Version 5.0 | 21 Mar 2025	Protocol version and date is updated.
	2-5	Please refer to the Table of Content in page 2-5	Please refer to the Table of Content in page 2-5	Page numbers are updated

	7	mg Microgram PBMC Peripheral Blood Memory Cell	µg Microgram mg Milligram mL Milliliter PBMC Peripheral Blood Mononuclear Cell	Abbreviation updated.
	10	Please refer to the list of figures in page 10	Please refer to the list of figures in page 10	Page numbers updated.
	15	Pregnancy-related AESIs include hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), intrauterine growth restriction, gestational diabetes mellitus, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, indicated preterm birth), chorioamnionitis, antepartum/postpartum hemorrhage, placenta abruption.	Pregnancy-related AESIs include hypertensive disorders of pregnancy (gestational hypertension, pre-eclampsia, pre-eclampsia with severe features including eclampsia), intrauterine growth restriction, gestational diabetes mellitus, pathways to preterm birth (premature preterm rupture of membranes, preterm labor, indicated preterm delivery), chorioamnionitis, antepartum/postpartum hemorrhage, placenta abruption.	Harmonized AESI term for maternal participants from indicated preterm birth to indicated preterm delivery.
	17	Qualitative assessment of anti-HEV IgM in breastmilk at delivery and among those who become infected with HEV*	Qualitative assessment of anti-HEV IgM in breastmilk at delivery and in serum samples among those who become infected with HEV*.	Updated to harmonize with SoE.
	17		* Additional blood samples (approximately 10ml for IgM testing and HEV RNA extraction) may be collected for RNA genotyping in participants diagnosed with HEV infection. The detailed procedure is outlined in a separate document entitled "Study-Specific Procedure (SSP) for HEV RNA Genotyping".	Blood samples specifically related to HEV infected participants were added.
	17	Preterm birth),	preterm delivery),	Harmonized AESI term for maternal participants from indicated preterm birth to indicated preterm delivery.
	20	3. Prior stillbirth or neonatal death, or multiple (≥ 3) spontaneous abortions.	3. Prior stillbirth or multiple (≥ 3) spontaneous abortions.	Neonatal death has been removed from the exclusion criteria, as it may be less directly related to the outcome of the current neonatal death. In contrast, other aspects of prior pregnancy history—such as stillbirth or spontaneous abortion—are considered more directly relevant

				pregnancy outcome that the rest of the criteria are maintained.
	21	* Participants receiving placebo will be provided with the 3 doses of Hecolin® or other available adult vaccines after the completion of infant visit to ensure equal benefit as the test vaccine group	* Participants receiving placebo will be provided with the 3 doses of Hecolin® or other available adult vaccines after the completion of infant visit, ensuring they have an equal opportunity to receive vaccination as the test vaccine group.	The wordings were updated for better clarity.
	22	The sample size for evaluating and comparing the pregnancy-related safety events among recipients of two doses of Hecolin® and a placebo is calculated using a precision-based approach. The bounds of the relative risk (rate ratio) of an event rate in the Hecolin® group divided by event rate in the placebo group, is assumed as 0.67 to 1.5. The sample sizes of 883 and 883 would provide a two-sided 95% confidence interval for the ratio of two event rates with a width that is equal to 0.83 which is 0.67 and 1.5 when the estimated event rates are 5% in each group and the ratio of two events is 1. The upper limit of the twosided 95% confidence interval of the relative risk lies below the upper bound (1.5). Given an event rate of 5%, the sample size of 883 pregnant participants who received the Hecolin® vaccine and 883 pregnant participants who received placebo will provide a 95% confidence interval with a width equal to 3.39% which are 5.45% and 8.83% and a width equal to 4.86% which are 4.85% and 9.71%, respectively. After accounting for a ~20% dropout rate, the study would require recruiting 1,104 pregnant participants who received the Hecolin® vaccine and 1,104 pregnant participants who received the placebo.	The sample size for evaluating and comparing the pregnancy-related safety events among recipients of two doses of Hecolin® and a placebo is calculated using a precision-based approach. The bounds of the relative risk (rate ratio) of an event rate in the Hecolin® group divided by event rate in the placebo group, is assumed as 0.67 to 1.5. The sample sizes of 883 and 883 would provide a two-sided 95% confidence interval for the ratio of two event rates with a width that is equal to 0.83 which is 0.67 and 1.5 when the estimated event rates are 5% in each group and the ratio of two events is 1. Given an event rate of 5%, the sample size of 883 pregnant participants who received IP will provide a 95% confidence interval with a width equal to 2.99% which are 3.66% and 6.65%. After accounting for a ~20% dropout rate, the study would require recruiting 1,104 pregnant participants who received the Hecolin® vaccine and 1,104 pregnant participants who received the placebo.	Information updated
	23	Laboratory Procedures/Evaluations for immunogenicity assessment For immunogenicity assessments, venous blood from the pregnant/non-pregnant participant, and infant blood sample (umbilical cord blood, capillary blood by heel stick and/or venous blood) will be collected for measuring the anti-HEV IgG antibodies. Whole blood will be centrifuged to obtain serum after collection. Sera obtained will be aliquoted and stored at -20°C in the central testing facility. Similarly, breastmilk will be expressed by hand into sterile containers and transported using cold chain to a central testing facility. The breastmilk will be aliquoted in conical tubes, centrifuged and skim off fatty layers and store at -20°C. Anti-HEV IgG in both samples types (serum and breastmilk) will be measured using commercially available Wantai HEV IgG ELISA assay (Beijing Wantai Biological Pharmacy Enterprise, Beijing, People's Republic of China) following manufacturer's instruction (for serum)	Laboratory Procedures/Evaluations for immunogenicity assessment For immunogenicity assessments, venous blood from the pregnant/non-pregnant participant, and infant blood sample (umbilical cord blood, capillary blood by heel stick and/or venous blood) will be collected for measuring the anti-HEV IgG and anti-HEV IgM antibodies. Whole blood will be centrifuged to obtain serum after collection. Sera obtained will be aliquoted and stored at -20°C in the central testing facility. Similarly, breastmilk will be expressed by hand into sterile containers and transported using cold chain to a central testing facility. The breastmilk will be aliquoted in conical tubes, centrifuged and skim off fatty layers and store at -20°C. Anti-HEV IgG in both samples types (serum and breastmilk) will be measured using commercially available Wantai HEV IgG ELISA assay (Beijing Wantai Biological Pharmacy Enterprise, Beijing, People's Republic of China) following manufacturer's instruction (for serum)	Ig M and the relevant details were added to match with the study end points.

		and as described in the study SOP (for breast milk); and results from quantitative ELISA will be reported in WHO Units (U/ml). This assay based on the principle of indirect ELISA uses the dimeric E2 antigen which retains the conformational epitopes present in HEV virions and in the HEV 239 used for HEV vaccine. A WHO reference serum will be used as a primary reference serum and anti-HEV IgG level determined after comparison with WHO reference serum. A portion of the blood from study participants will be subjected to additional assays as part of routine screening for pregnant women as per the national guidelines/practice and required by the study as described in the study protocol. IVI Lab liaison will provide lab quality oversight throughout the study period to ensure high quality results	and as described in the study SOP (for breast milk); and results from quantitative ELISA will be reported in WHO Units (U/ml). Similarly, anti-HEV IgM will be measured in both sample types (serum and breastmilk) using commercially available Wantai HEV IgM ELISA assay following the manufacturer's instruction (for serum) and as described in the study SOP (for breast milk). This assay based on the principle of indirect ELISA uses the dimeric E2 antigen which retains the conformational epitopes present in HEV virions and in the HEV 239 used for HEV vaccine. A WHO reference serum will be used as a primary reference serum and anti-HEV IgG level determined after comparison with WHO reference serum. A portion of the blood from study participants will be subjected to additional assays as part of routine screening for pregnant women as per the national guidelines/practice and required by the study as described in the study protocol. IVI Lab liaison will provide lab quality oversight throughout the study period to ensure high quality results.	
	25	1.3 TABLE OF STUDY PROCEDURE/SCHEDULE OF EVENTS Table 2. Schedule of Study Procedures/Schedule of Events (SOE) 	1.3 TABLE OF STUDY PROCEDURE/SCHEDULE OF EVENTS Table 2. Schedule of Study Procedures/Schedule of Events (SOE) 	Window for delivery widened.
	26	g.A full physical examination will be performed at screening, delivery (V5), and UV, and targeted physical examinations will be followed for the subsequent visits. h.Will be performed in non-pregnant participants only.	g.Full physical examinations will be performed at screening and delivery (V5), and targeted physical examinations will be conducted during subsequent visits. For unscheduled visit, an attending physician will decide suitable physical examination method based on his/her judgement. h. Will be performed in non-pregnant participants. For pregnant participants, if V6 is scheduled 6 weeks or later after delivery, a urine pregnancy test will be performed.	Details on targeted physical examinations were added. Urine pregnancy test is added for pregnant participants. to screen the second pregnancy before receiving the third dose.
	26	Table 3. Study Procedures/Schedule of Events for infant participants 	Table 3. Study Procedures/Schedule of Events for infant participants 	Visit window for infant participants is widened.
	27	f. Full physical examination will be performed at all scheduled visits. For unscheduled visit, physician will decide suitable physical examination method based on his/her judgment.. g. Bayley Scales of Infant and Toddler Development™, fourth edition (BayleyTM-4) will be used for developmental assessment. (5) h. Samples for immunogenicity assessment will be taken from infants born from pregnant immunogenicity subsets (n=150) of arm I and 2. i. An infant blood draw should be preferentially obtained within 24 hours of birth if cord blood is not collected at delivery, but is permissive up to 72 hours post-delivery	f. Full physical examinations will be performed at all scheduled visits. For unscheduled visit, an attending physician will decide suitable physical examination method based on his/her judgment. g. Bayley Scales of Infant and Toddler Development™, fourth edition (Bayley™-4) will be used for developmental assessment. (5) h. Samples for immunogenicity assessment will be taken from infants born from pregnant immunogenicity subsets (n=150) of arm I and 2. i. An infant blood draw should be preferentially obtained within 24 hours of birth if cord blood is not collected at delivery, but is permissive up to 7 days post-delivery.	Window widened for samples related to delivery.

	33	The result showed that overall in 436 Hecolin® recipients during or within 90 days before pregnancy, the rate of spontaneous abortion was 8% compared to 4% in the 484 Hepatitis B vaccine (control vaccine) recipients (p=0.021). And overall in 238 Hecolin® recipients during pregnancy, the rate of spontaneous abortion was 10.5% compared to 5.3% in the 292 Hepatitis B vaccine recipients. No association was seen between Hecolin® receipt and fetal loss, stillbirth or elective termination among women vaccinated more than 90 days prior IVI_Hecolin_P001_Protocol_V4.0_25Ju n2024 CONFIDENTIAL Page | 34 to date of LMP. This analysis is unpublished. iv) Vaccination coverage and adverse events following a reactive vaccination campaign against hepatitis E in Bentiu displaced persons camp, South Sudan. Campaigns using Hecolin have been implemented in South Sudan. Those prioritized include residents aged 16-40 years in camps for internally-displaced persons, including pregnant women. The result indicated no evidence of increased risk of fetal lost (spontaneous abortion or stillbirth) among Hecolin® vaccinated women. (39	The result showed that among pregnant participants, the Hecolin® group had a higher risk of miscarriage (136 [5·7%] of 2407 pregnant participants) compared with the control group, Hepa-B, a hepatitis B vaccine (102 [3·9%] of 2604; adjusted odds ratio 1·54 [95% CI 1·15–2·08]). (39) iv) Vaccination coverage and adverse events following a reactive vaccination campaign against hepatitis E in Bentiu displaced persons camp, South Sudan. Campaigns using Hecolin have been implemented in South Sudan. Those prioritized include residents aged 16-40 years in camps for internally-displaced persons, including pregnant women. The result indicated no evidence of increased risk of fetal lost (spontaneous abortion or stillbirth) among Hecolin® vaccinated women. (40)	The Bangladesh study result updated to reflect the recent publication result.
	44	This trial will be conducted at Clinical Trial Unit at Aga Khan University (AKU) Hospital in Karachi, Pakistan. The participants will be recruited from 4 referral centers under management of the Department of Pediatrics and Child Health of the Aga Khan University. The delivery site will include Aga Khan Hospital for Women and Children, Kharadar.	This trial will be conducted at Clinical Trial Unit at Aga Khan University (AKU) Hospital in Karachi, Pakistan. The participants will be recruited from 4 referral centers under management of the Department of Pediatrics and Child Health of the Aga Khan University. Based on the enrollment status, the recruitment sites may be extended within Karachi including Kharadar hospital. The delivery site will include Aga Khan Hospital for Women and Children, Kharadar.	Site extension plan to include Kharadar site for enrollment is added.
	44	All laboratory assays including screening labs and immunogenicity assessment will be performed at AKU. Some tests may be outsourced to other laboratories under the responsibility of IVI if required.	All laboratory assays including screening labs and immunogenicity assessment will be performed at AKU. In the case of home delivery, samples may be collected at the referral sites or through home visits. Some tests may be outsourced to other laboratories under the responsibility of IVI, if required.	Venue widened in collecting samples for home delivery.
	46	For the immunogenicity subset, the participants' blood will be drawn before and 4 weeks post each dose of IP injection. Breast milk and maternal blood samples will be taken at delivery, 6 weeks, and 24 weeks after delivery.	The final blood sample from the maternal participant will be drawn 24 weeks after the third dose injection. Breast milk and maternal blood samples will be taken at delivery, 6 weeks, and 24 weeks after delivery.	The description related to final blood sampling added for clarity.
	47			Figure 1 relocated within the section to reduce blank space.

	57	• Neonates born from the maternal participants who are immunogenicity subset, umbilical cord blood (approximately 10mL), will be collected for immunology assessment. (Venous blood 1 to 3 ml or capillary blood by heel stick will be collected if cord blood is not available for collection within 72 hours) • Any neonate unsolicited AE/SAE/AESIs will be documented. • Information those are to be collected related to delivery visit and procedures including blood and breast milk sampling will be obtained within 3 days window	• Neonates born from the maternal participants who are immunogenicity subset, umbilical cord blood (approximately 10mL), will be collected for immunology assessment. (Venous blood 1 to 3 ml or capillary blood by heel stick will be collected if cord blood is not available) • Any neonate unsolicited AE/SAE/AESIs will be documented. • Information those are to be collected related to delivery visit and procedures including blood and breast milk sampling will be obtained within 1 day at delivery, but is permissive up to 7 days post-delivery.	Window widened for postpartum samples for delivery.
	65	3. Prior stillbirth or neonatal death, or multiple (≥ 3) spontaneous abortions.	3. Prior stillbirth or multiple (≥ 3) spontaneous abortions.	Prior stillbirth history deleted from exclusion criteria.
	80	Receipt of immunoglobulins and/or any blood (including red blood cells, plasma and/or platelets transfusion) or blood products through 4 weeks after the last study vaccination	Receipt of immunoglobulins and/or any blood (including red blood cells, plasma and/or platelets transfusion) or blood products through 4 weeks after the last study vaccination (with the exception of safety subset).	For safety subset, taking immunoglobulins and/or any blood or blood product will not be considered as receiving prohibited medication.
	86	Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions)	Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and/or convenience admissions, prophylactic phototherapy for physiological jaundice)	Details added specific to the pregnant/infant participants.
	87,89,101	preterm birth	preterm delivery	Harmonized AESI term for maternal participants from indicated preterm birth to indicated preterm delivery.
	91	All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of hospitalization planned before inclusion into the study, not a 24-hour stay or emergency room visit or out-patient treatment with no hospitalization. Hospitalization for delivery represents normal obstetrical care is not an SAE.	All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of hospitalization planned prior to study inclusion, hospital stays of less than 1 day for non-pregnant participants, and up to 3 days observation for pregnant participants), emergency room visit or out-patient treatment with no hospitalization. Hospitalization for delivery and/or post-partum/newborn care as a part of normal obstetrical/infant care is not an SAE. If a pregnant	Specific observational period for pregnant participants is added reflecting clinical practice at the site. Also, considering the participants being pregnant/newborn, details to differentiate hospitalization due to abnormal condition and normal postpartum condition is added.

	93-94	10.2.2 Relationship to Investigational Product For all collected AEs, the clinician who examines and evaluates the participant will determine the relationship of each AE with the investigational product based on plausible biologic mechanism, temporal relationship of occurrence after administration of the investigational product, identification of possible alternative etiologies including underlying disease, concurrent illness or concomitant medication, and his/her clinical judgment. The relationship of vaccination to AE will be determined based on the definitions below. Not related: The AE is clearly or most probably caused by other etiologies such as participant's underlying condition, therapeutic intervention, or concomitant therapy; or the delay between vaccination and the onset of the AE is incompatible with a causal relationship; or the AE started before the first vaccination. Related: There is a "reasonable possibility" that the AE was caused by the vaccine, meaning that there is evidence or arguments to suggest a causal relationship. The same definitions are used for assessing the relationship between vaccination and SAEs	**10.2.2 Relationship to Investigational Product** For all collected AEs, the investigator or a qualified sub-investigator will assess and determine the relationship of each AE with the investigational product based on his/her best medical judgement considering plausible biologic mechanism, temporal relationship of occurrence after administration of the investigational product, identification of possible alternative etiologies including underlying disease, concurrent illness or concomitant medication. The relationship of vaccination to AE will be determined based on the definitions below. {Madhi, 2020 #99} **Definitely Related** • Follows a reasonable temporal sequence from administration of the test vaccine. • Consistent with known actions of the test vaccine or product class. • Cannot be reasonably explained by known characteristics of the maternal or infant participant's (as applicable) clinical state, common intercurrent illnesses, or other treatments administered to the maternal participant. • May be confirmed by re-challenge (if applicable). • Strongest level of causality with clear evidence linking the AE to the test vaccine, and no alternative explanations. **Probably Related** • Follows a reasonable temporal sequence from administration of the test vaccine. • Based on known or suspected actions of the test vaccine or product class, a plausible mechanism could exist. • Cannot be reasonably explained by known characteristics of the maternal or infant participant's (as applicable) clinical state, common intercurrent illnesses, or other treatments administered to the maternal participants. • Maybe supported by a clinical or laboratory evidence. • Strong likelihood of causality but lacks direct confirmation through re-challenge or indisputable evidence. **Possibly Related** • Follows a reasonable temporal sequence from administration of the test vaccine. • Based on known or suspected actions of the test vaccine or product class, a plausible mechanism could exist. • May be reasonably explained by known characteristics of the maternal or infant participant's (as	The criteria for causal assessment were added based on the comments from DRAP (Pakistan regulatory authority) / NBC.

			applicable) clinical state, common intercurrent illnesses, or other treatments administered to the maternal subject; but the Investigator deems this less likely than test vaccine effect. • Causality is suspected but not strongly supported, and alternative explanations remain plausible. **Unrelated/Unlikely To Be Related** • May or may not follow a reasonable temporal sequence from administration of the test vaccine. • No plausible mechanism based on known or suspected actions of the test vaccine or product class. • Readily explained by known characteristics of the maternal or infant participant's (as applicable) clinical state, common intercurrent illnesses, or other treatments administered to the maternal subject. The definitions, Definitely Related, Probably Related, Possibly Related, can be considered as adverse drug reaction (ADR) and Unrelated/Unlikely To Be related can be considered as Non-ADR for analysis.	
	105	The sample size for evaluating and comparing the pregnancy-related safety events among recipients of two doses of Hecolin® and placebo is calculated using a precision-based approach. The bounds of the relative risk (rate ratio) of an event rate in the Hecolin® group divided by the event rate in the placebo group, is assumed as 0.67 to 1.5. The sample sizes of 883 and 883 would provide a two-sided 95% confidence interval for the ratio of two event rates with a width that is equal to 0.83 which is 0.67 and 1.5 when the estimated event rates are 5% in each group and the ratio of two events is 1. The upper limit of the two-sided 95% confidence interval of the relative risk lies below the upper bound (1.5). Given an event rate of 5%, the sample size of 883 pregnant participants who received the Hecolin® vaccine and 883 pregnant participants who receive placebo will provide a 95% confidence interval with a width equal to 3.39% which are 5.45% and 8.83% and a width equal to 4.86% which are 4.85% and 9.71%, respectively	The sample size for evaluating and comparing the pregnancy-related safety events among recipients of two doses of Hecolin® and placebo is calculated using a precision-based approach. The bounds of the relative risk (rate ratio) of an event rate in the Hecolin® group divided by the event rate in the placebo group, is assumed as 0.67 to 1.5. The sample sizes of 883 and 883 would provide a two-sided 95% confidence interval for the ratio of two event rates with a width that is equal to 0.83 which is 0.67 and 1.5 when the estimated event rates are 5% in each group and the ratio of two events is 1. Given an event rate of 5%, the sample size of 883 pregnant participants who received the IP will provide a 95% confidence interval with a width equal to 2.99% which are 3.66% and 6.65%.	Information updated
	107	The statistical hypothesis for comparison safety endpoint is: • H0 (null hypothesis): the bound of AESIArm 1 / AESIArm 2 > 1.5 • H1 (alternative hypothesis): the bound of AESIArm 1 / AESIArm 2 ≤ 1.5, where Arm 1 and 2 represent pregnant women receiving Hecolin® and placebo, respectively.		Removed the statements of statistical hypothesis testing.
	108	The Phase II study will be considered to meet the primary immunogenicity objective, the pregnant women group is non-inferior to the non-pregnant women	The Phase II study will be considered to meet the primary immunogenicity objective, the pregnant women group is non-inferior to the non-pregnant women	Information added

		group if the lower limit of the 95% confidence interval lies above non-inferior bound 0.67. The non-inferior test will be performed at a 2.5% significance level using a one-sided test (equivalently, a significance level of 5% using a two-sided test). If the upper limit of the two-sided 95% confidence interval of the relative risk lies below the upper bound (1.5), then it will be considered to meet the primary safety objective	group if the lower limit of the 95% confidence interval lies above non-inferior bound 0.67. The non-inferior test will be performed at a 2.5% significance level using a one-sided test (equivalently, a significance level of 5% using a two-sided test). If the width of confidence interval is within 0.83, then it will be considered to meet the primary safety objective.	
	108	The FAS is a modified intention to treat (mITT) analysis set that includes all participants who receive at least one dose of Hecolin® or Placebo and have at least one post-baseline immunogenicity data available. The immunogenicity endpoints will be analyzed using the FAS.	The FAS is a modified intention to treat (mITT) analysis set that includes all participants who receive at least one dose of Hecolin® or Placebo and have at least one post-baseline immunogenicity data available. The immunogenicity endpoints will be analyzed using the FAS. A sensitivity analysis using the FAS will be conducted for the immunogenicity endpoints.	Updated to align with the analysis described in synopsis.
	108-109	The PPS is comprised of a subset of the FAS who receive all their planned administrations and who have no SMM-assessed important protocol deviations. The major protocol deviations are listed in Section 7.2.15 Protocol Deviations. Participants excluded from the PPS will be identified and documented before the final database lock through the analysis dataset review meeting. A sensitivity analysis using the PPS will be conducted for the immunogenicity endpoints.	The PPS is comprised of a subset of the FAS who receive all their planned administrations and who have no SMM-assessed important protocol deviations. The major protocol deviations are listed in Section 7.2.15 Protocol Deviations. Participants excluded from the PPS will be identified and documented before the final database lock through the analysis dataset review meeting.	Deleted sentence to align with analysis described in synopsis.
	110-111	The immunogenicity endpoints analysis will be conducted on the FAS and the sensitivity analysis using the PPS will be conducted. For anti-HEV IgG ELISA, the GMC and GMFR with its associated 95% CI are calculated as the antilogarithmic of the difference and its 95% CI between the mean of the log-transformed data in Arm 1 and that in Arm 3 with adjustment for serostatus at baseline and baseline titer in a general linear regression model. The participants' age will be adjusted for the analysis if there is a significant difference in age between Arm 1 and Arm 3. The SCR (seroconversion is defined as at least 4-fold increase from baseline) difference and its associated 95% CI are calculated between the SCR in Arm 1 and that in Arm 3.	The immunogenicity endpoints analysis will be conducted on both the PPS and FAS, and the sensitivity analysis using the FAS will be conducted. For anti-HEV IgG ELISA, the GMC and GMFR with its associated 95% CI are calculated as the antilogarithmic of the difference and its 95% CI between the mean of the log-transformed data in Arm 1 and that in Arm 3 with adjustment for serostatus at baseline and baseline titer in a general linear regression model. The participants' age will be adjusted for the analysis if there is a significant difference in age between Arm 1 and Arm 3. The SCR (seroconversion is defined as at least 4-fold increase from baseline) difference and its associated 95% CI are calculated between the SCR in Arm 1 and that in Arm 3.	Updated to align with analysis described in synopsis.
	111	12.5.7 Additional Sub-Group Analysis The subgroup analysis will be carried out to assess the immunogenicity and safety depending on the baseline serostatus. The potential difference in safety and immunogenicity coming from gestational age will be assessed for pregnant participants by trimester sub-group analysis	**12.5.7 Additional Sub-Group Analysis** The subgroup analysis will be carried out to assess the immunogenicity and safety depending on the baseline serostatus. The potential difference in safety and immunogenicity coming from various factors, including but not limited: gestational age will be assessed for pregnant participants by trimester sub-group analysis.	Added factors that could potentially account for differences.

	126	As the pregnant women show increased respiratory rate by 2-4 breaths/minute, the rates in grading has been adjusted. Reference from	As the pregnant women show increased respiratory rate by 2-4 breaths/minute, the rates in grading has been adjusted. Reference from <Research on vaccine during pregnancy: Reference values for vital signs and laboratory assessments, Vaccine. 2013 Sep 13;31(40):4264-73(57).	Reference updated.
Document Type (eg. Protocol, ICF)	**Page**	**Before**	**After**	**Rationale for the Change**
CRF	1	**Document ID:** **IVI_Hecolin_P001_CRF V4.**	**Document ID:** **IVI_Hecolin_P001_CRF V5.**	Document information update
CRF	2	VERSION HISTORY Version 1.0 — Date: 10Nov2022 — Description of Changes: Based on Protocol V1.0 dated 27Oct20 2.0 — 17Feb2023 — Based on Protocol V2.0 dated 03Feb20 3.0 — 22May2023 — Based on Protocol V3.0 dated 10May2 4.0 — 04Jul2024 — Update based on Protocol V4.0 dated 2 match system design 4.1 — 06Aug2024 — Update prenatal information form, dem baseline characteristics form, and recor	+ VERSION HISTORY Version 1.0 — Date: 10Nov2022 — Description of Changes: Based on Protocol V1.0 dated 27Oct20 2.0 — 17Feb2023 — Based on Protocol V2.0 dated 03Feb20 3.0 — 22May2023 — Based on Protocol V3.0 dated 10May2 4.0 — 04Jul2024 — Update based on Protocol V4.0 dated 2 match system design 4.1 — 06Aug2024 — Update prenatal information form, dem baseline characteristics form, and recor 5.0 — 28Mar2025 — Based on Protocol V5.0 dated 21Mar20	Added version 5 description of change
CRF	All pages footnote	IVI Hecolin P001 CRF, Version 4.1 Dated 0	IVI Hecolin P001 CRF, Version 5.0 Dated 2	Footnote date and version update
CRF	3	Schedule of Study Procedures/Schedule of Events (SoE) Visit Number: V1 | V2 | IPV PCV* | V3 | IPV PCV* | V4 | V5 | V6 | IPV PCV* Visit Day: -14 to 0 | 0 | 7 | 28 | 56 | 84 | Delivery | 168 | 170 Visit Week (W): -2 to 0 | 0 | 1 | 4 | 8 | 12 | - | 24 | 25 Visit Month (M): - | 0 | - | 1 | - | 2 | - | 6 | - Visit Window: - | - | +3D | +7D | +3D | +7D | +3D | +7D | +3D	Schedule of Study Procedures/Schedule of Events (SoE) Visit Number: V1 | V2 | IPV PCV* | V3 | IPV PCV* | V4 | V5 | V6 | IPV PCV* Visit Day: -14 to 0 | 0 | 7 | 28 | 56 | 84 | Delivery | 165 | 170 Visit Week (W): -2 to 0 | 0 | 1 | 4 | 8 | 12 | - | 24 | 25 Visit Month (M): - | 0 | - | 1 | - | 2 | - | 6 | - Visit Window: - | - | +3D | +7D | +3D | +7D | +7D* | +7D | +3D	Visit window V5 updated per protocol V5.0
CRF	4	g. A full physical examination will be performed at screening, delivery (V5), and CV, and targeted physical examinat subsequent visits h. Will be performed in non-pregnant participants only	g. Full physical examinations will be performed at screening and delivery (V5), and targeted physical examinatio subsequent visits. For unscheduled visit, an attending physician will decide suitable physical examination method h. Will be performed in non-pregnant participants. For pregnant participants, if V6 is scheduled 6 weeks or later afte test will be performed	Footnote g and h of SoE updated per protocol V5.0
CRF	7	1) X: Referral Center Code; 1= AG (Ali Akbar Shah), 2= BH (Bhains Colony), 3= IH (Ibrahim Hy 2) YYYY: Sequence number; 0001, 0002, 0003, ... E.g. 53-0001 for the first participant at the IH (Ibrahim Hydari) site	1) X: Referral Center Code; 1= AG (Ali Akbar Shah), 2= BH (Bhains Colony), 3= IH (Ibrahim Hydari), KH(Khairpur) 2) YYYY: Sequence number, 0001, 0002, 0003, ... E.g. 53-0001 for the first participant at the IH (Ibrahim Hydari) site	Add new referral center and assigned referral center code
CRF	14	**Delivery outcome**	**Delivery outcome**	Option label update
CRF	14	→ If 'Yes', please select the following diagnosis (multiple choice) ○ Preterm labor ○ Premature preterm ru ○ Indicated preterm bir	→ If 'Yes', please select the following diagnosis (multiple choice) ○ Preterm labor ○ Premature preterm ○ Indicated preterm d	Option label update
CRF	24	Mode of delivery ○ Normal vaginal delive ○ Instrumented vaginal ○ Elective cesarean sect ○ Emergency cesarean s ○ Vaginal delivery after	Mode of delivery ○ Normal vaginal delivery ○ Instrumented vaginal deli ○ Elective cesarean section ○ Emergency cesarean secti ○ Vaginal delivery after ces	Correct wording for consistency.
CRF	24	NA	→ If elective or emergency cesarean section is performed, please select the reason ○ Previous cesarean section ○ Fetal malpresentation (e.g. bree ○ Fetal distress ○ Obstructed labor ○ Failure of labor progression ○ Placenta previa ○ Placental abruption ○ Severe preeclampsia or eclamp ○ Cord prolapse ○ Uterine rupture ○ Fetal macrosomia ○ Fetal congenital anomaly ○ Other (Please specify) → If 'Other', please specify	Add reasons when cesarean section is performed.
CRF	24	Were there any delivery complications? ○ Yes ○ No → If 'Yes', please specify:	Were there any delivery complications? ○ Yes ○ No → If 'Yes', please specify:	Design update

CRF	24	Was there any abnormal postpartum hemorrhage: ○ Yes ○ No Current concomitant medications and treatments were checked?: ○ Yes ○ No Was maternal blood collected? (8mL)*: ○ Yes ○ No Was breast milk collected? (10mL)*: ○ Yes ○ No → If any above 2 questions were marked 'No', please provide the reason.: ○ Woman delivered at home (with ○ Team was not informed within ○ Woman delivered at any other area) ○ Woman or family refused sampl ○ Woman passed away before san ○ Other →If 'Other', please specify Were vital signs (Vital signs form) measured?: ○ Yes ○ No →If 'No', please specify the reason	NA	Fields removed
CRF	25	→ If 'Single', fill out the following questions. → If 'Multiple', fill out the following questions for each infant delivered. Delivery outcome of the neonate: ○ Alive ○ Dead Fetal presentation at delivery: ○ Cephalic ○ Transverse ○ Breech ○ Unknown Placenta condition: ○ Normal ○ Abnormal ○ Unknown	Delivery outcome of the neonate: ○ Live ○ Dead Fetal presentation at delivery: ○ Cephalic ○ Transverse ○ Breech ○ Unknown Placenta condition: ○ Normal ○ Abnormal ○ Unknown	3 fields moved from 12.1 to 12.2
CRF	25	→If 'No', please specify the alternative blood sample collection method: ○ Heel prick ○ Venous blood (if heel prick h successful) ○ Not collected	→If 'No', please specify the alternative blood sample collection method: ○ Heel prick ○ Venous blood (if heel prick b successful) ○ Not collected ○ Not collected, participant in ge	Added options for participant in general cohort.
CRF	25	→If 'ND' was entered to any of the APG scores, please specify the reasons	→If 'ND' was entered to 1 or 5 minutes of the APGAR scores, please specify the reasons	Updated the condition for APGAR scores collection
CRF	27-28	16.1 Laboratory Test - Screening(V1) Was the prenatal care laboratory conducted within 14 days of the screening visit?: ○ Yes ○ No → If 'Yes', please fill the result in the corresponding laboratory forms. (Secology, Blo Chemistry, Urinalysis) → If 'No', please collect the sample for screening laboratory test and fill the following Was the blood sample collected for laboratory test?: ○ Yes ○ No → If 'No', please specify the reason → If 'Yes', please specify the details below. Date of blood sample collection (e.g., 23-Jan-2023): DD-MMM-YYYY Sample ID*: [Type][Sample Type]-[Visits]-[I Actual blood Collection Volume (e.g., 10.0 mL): ___ ___ . ___mL Was the urine sample collected for laboratory test?: ○ Yes ○ No → If 'No', please specify the reason → If 'Yes', please specify the date of urine sample collection (e.g., 23-Jan-2023): DD-MMM-YYYY Sample ID*: [Type][Sample Type]-[Visits]-[I	16.1 Laboratory Test - Screening(V1) Was the prenatal care laboratory conducted within 14 days of the screening visit?: ○ Yes ○ No → If 'Yes', please fill the Date of blood sample collection – ANC, Date of urine sampl and Was there another sample collection done at screening? Date of blood sample collection – ANC: DD-MMM-YYYY Date of urine sample collection – ANC: DD-MMM-YYYY → If 'No', please collect the sample for screening laboratory test and fill the following Was the blood sample collected for laboratory test?: ○ Yes ○ No → If 'No', please specify the reason → If 'Yes', please specify the details below. Date of blood sample collection – screening (e.g., 23-Jan-2023): DD-MMM-YYYY Sample ID*: [Type][Sample Type]-[Visits]-[I Actual blood Collection Volume (e.g., 10.0 mL): ___ ___ . ___mL Was the urine sample collected for laboratory test?: ○ Yes ○ No → If 'No', please specify the reason → If 'Yes', please specify the details below. Date of urine sample collection – screening (e.g., 23-Jan-2023): DD-MMM-YYYY Sample ID*: [Type][Sample Type]-[Visits]-[I Was there another sample collection done at screening?: ○ Yes ○ No → If 'Yes', please fill the Date of blood sample collection – additional and Date of urin - additional Date of blood sample collection – additional: DD-MMM-YYYY Date of urine sample collection – additional: DD-MMM-YYYY	Added additional date of sample collection when samples were collected separately for different purpose.
CRF	35	3. Prior stillbirth or neonatal death, or multiple (≥ 3) spontane	3. Prior stillbirth or multiple (≥ 3) spontaneous abortions.	Updated exclusion criterion per protocol V5.0
CRF	39	Enrollment ID: EXY-ZSSSS-F where 1) X: Cohort code; G=general cohort, M= Immune cohort. 2) Y: Referral Center code; 1= AG (Ali Akbar Shah), 2= BH (Bhains Colony), 3= IH (Ibrahim Hyd	Enrollment ID: EXY-ZSSSS-F where 1) X: Cohort code; G=general cohort, M= Immune cohort. 2) Y: Referral Center code; 1= AG (Ali Akbar Shah), 2= BH (Bhains Colony), 3= IH (Ibrahim Hyd 5= KH(Kharaisir).	Added new referral center code to enrollment ID.

CRF	41	**21.2 Immediate Adverse Event** -V2 (W0), V3 (W4), V6 (W24) **Immediate Adverse Event 30 mins Post Vaccination** **If any treatment or medication is taken for the symptoms, please record details in 'Concomitant Medication' form.** **Please enter details if the immediate adverse event has occurred within 30 mi administration.** **Please record all solicited adverse events after 30 minutes in 'Solicited Adverse Event'** **Solicited Event Term** [AE Term] **Severity within 30 minutes** ○ Mild (Grade1) ○ Moderate (Grade2) ○ Severe (Grade3) ○ Potentially Life-threatening (Grade **Relatedness to investigational product** ○ Related ○ Not Related	**21.2 Immediate Adverse Event** -V2 (W0), V3 (W4), V6 (W24) **Immediate Adverse Event 30 mins Post Vaccination** **If any treatment or medication is taken for the symptoms, please record details in 'Concomitant Medication' form.** **Please enter details if the immediate adverse event has occurred within 30 m administration.** **Please record all solicited adverse events after 30 minutes in 'Solicited Adverse Event'** **Solicited Event Term** [AE Term] **Severity within 30 minutes** ○ Mild (Grade1) ○ Moderate (Grade2) ○ Severe (Grade3) ○ Potentially Life-threatening (Grade **Relatedness to investigational product** ○ ~~Definitely Related~~ ○ Probably Related ○ Possibly Related ○ Unrelated/Unlikely to be Related	Immediate AE added causality options per protocol V5.0
CRF	43	**Maximum severity after Day 6?** ○ None (Grade0) ○ Mild (Grade1) ○ Moderate (Grade2) ○ Severe (Grade3) ○ Potentially Life-threatening (Grade **Relatedness to investigational product** ○ Related ○ Not Related	**Maximum severity after Day 6?** ○ None (Grade0) ○ Mild (Grade1) ○ Moderate (Grade2) ○ Severe (Grade3) ○ Potentially Life-threatening (Grade **Relatedness to investigational product** ○ ~~Definitely Related~~ ○ Probably Related ○ Possibly Related ○ Unrelated/Unlikely to be Related	Solicited AE added causality options per protocol V5.0
CRF	44, 58	**Relatedness to investigational product**	**Relatedness to investigational product** ○ ~~Definitely~~ ○ Probably R ○ Possibly R ○ Unrelated	Unsolicited AE added causality options per protocol V5.0
CRF	45	**Is this an Adverse Event of Special Interest (AESI)? *** ***If 'Yes' was checked under AESI on the 'Unsolicited Adverse Event form', please fill a EACH AESI case reported based on the criteria below. If the AESI case is an SAE case 'SAE form' only.***	**Is this an Adverse Event of Special Interest (AESI)? *** ***If 'Yes' was checked under AESI on the 'Unsolicited Adverse Events form', AESI form for EACH AESI case reported based on the criteria below.***	Description update on reporting AESI
CRF	46-47	1. Hypertensive disorders of pregnancy: - Gestational hypertension: - Systolic Blood pressure >= 140 and/or diastolic blood pressure >= 90 mmHg for the first time after 20 weeks without proteinuria - Pre-eclampsia Systolic Blood pressure >= 140 and/or diastolic blood pressure >= 90 mmHg after 20 weeks in previously normotensive women with prote protein: creatinine ratio ≥ 0.3, or Dipstick 1+ persistent, or with : • Thrombocytopenia (Platelet count < 100,000/ µL) • Renal insufficiency (Creatinine level > 1.1 mg/dL or doubling of baseline (in prior renal disease)) • Liver involvement (Serum transaminase levels (AST or ALT) twice normal) • Cerebral symptoms (Headache, visual disturbances, convulsions) • Pulmonary edema - Eclampsia: All components of pre-eclampsia with a new-onset seizure 2. Placenta abruptions: Separation of placenta from the uterus with bleeding (concealed or vaginal) 3. Intrauterine growth restriction: Fetal estimated weight or abdominal circumference is below the 10th percentile for gestational age. 4. Gestational diabetes mellitus: Gestational diabetes mellitus is defined if one or more of the following criteria are met. Plasma glucose / Glucose concentration threshold Mmol/L / Mg/dl Fasting 5.1-6.9 / 92-125 1-hour OGTT ≥ 10.0 / 180 2-hour OGTT 8.5-11.0 / 153-199 a. One or more of these values from a 75 g OGTT must be equaled or exceeded for the diagnosis of gestational diabetes. *OGTT = oral glucose tolerance test 5. Pathways to preterm birth - Premature preterm rupture of membranes(Membrane rupture before labor that occurs before 37 completed weeks) - Preterm labor(Regular contractions before 37 weeks that are associated with cervical change) - Indicated preterm birth(Labor which is induced or in which the infant is delivered by cesarean section for maternal or fetal illness.) 6. Chorioamnionitis: Isolated maternal fever between 38.0°C or higher with no additional risk factors present, and with or without persistent temperature ele 7. Hemorrhage - Antepartum: Bleeding during third trimester - Postpartum: Cumulative blood losses of approximately > 1,000 mL or blood loss accompanied by signs and symptoms of hypovolemia	1. Gestational hypertensions: Systolic Blood pressure >= 140 and or diastolic blood pressure >= 90 mmHg for the first time after 20 weeks without proteinuria 2. Pre-eclampsia Systolic Blood pressure >= 140 and or diastolic blood pressure >= 90 mmHg after 20 weeks in previously normotensive women with pro Urine protein: creatinine ratio ≥ 0.3, or Dipstick 1+ persistent, or with : • Thrombocytopenia (Platelet count < 100,000/ µL) • Renal insufficiency (Creatinine level > 1.1 mg /dL or doubling of baseline (in prior renal disease)) • Liver involvement (Serum transaminase levels (AST or ALT) twice normal) • Cerebral symptoms (Headache, visual disturbances, convulsions) • Pulmonary edema 3. Eclampsia: All components of pre-eclampsia with a new-onset seizure 4. Placenta abruptions: Separation of placenta from the uterus with bleeding (concealed or vaginal) 5. Intrauterine growth restriction: Fetal estimated weight or abdominal circumference is below the 10th percentile for gestational age 6. Gestational diabetes mellitus: Gestational diabetes mellitus is defined if one or more of the following criteria are met. Plasma glucose / Glucose concentration threshold Mmol/L / Mg/dl Fasting 5.1-6.9 / 92-125 1-hour OGTT ≥ 10.0 / 180 2-hour OGTT 8.5-11.0 / 153-199 a. One or more of these values from a 75 g OGTT must be equaled or exceeded for the diagnosis of gestational diabetes. *OGTT = oral glucose tolerance test 7. Premature rupture of membranes: Membrane rupture before labor that occurs before 37 completed weeks 8. Preterm labor: Regular contractions before 37 weeks that are associated with cervical change 9. Indicated preterm delivery Labor which is induced or in which the infant is delivered by cesarean section for maternal or fetal illness. 10. Chorioamnionitis: Isolated maternal fever between 38.0°C or higher with no additional risk factors present, and with or without persistent temperature e 11. Hemorrhage - Antepartum: Bleeding during third trimester - Postpartum: Cumulative blood losses of approximately > 1,000 mL or blood loss accompanied by signs and symptoms of hypovolemia	AESI definition level update
CRF	48,61	3. All medical events leading to hospitalizations will be recorded and reported as SAEs, with the exception of hospitalizations planned prior to study entry (e.g. non-pregnant participants and up to 6 days observation for pregnant participants), emergency room visit or out-patient treatment with no hospitalization. If a participant receives care as a part of normal obstetrical infant care it will not be SAE. If a pregnant participant gets sick during the observation period, the observation period will be extended to include prolonged hospitalization. 4. "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.		AESI footnote update per protocol V5.0
CRF	49	→ If 'Yes', please specify the details below. → After D28 from each vaccination, concomitant medication history related to SAEs	→ If 'Yes', please specify the details below. → After D28 from each vaccination, concomitant medication history related to AESIs/SAEs	Added AESI for concomitant medication reporting.
CRF	51	Visit Number / Visit Weeks / Visit Window / Infant Enrollment ID Assignment* / Document APGAR Score, Gestational Age at Birth* / Gross Anomaly Check / Demographic Information / Weight / Length / Head Circumference / Medical History* / Concomitant Medications* / Physical Examination* / Vital Signs / Developmental Assessment# / Blood Samples for Immunogenicity* (Cord Blood / Venous Blood) / Safety Follow Up* / Study Completion Form a. In case of home delivery, procedures can be conducted within 3 days window. b. The participant card will be given to the parent/guardian of the infant participant at the delivery visit. c. APGAR score measured at 1, 5 and 10 minutes will be collected. d. Any medical history during fetal period (e.g. anomaly detected by ultrasonography, fetal treatment conducted). e. Concomitant medications related to AE/AESI/SAE will be collected. f. Full physical examinations will be performed at all scheduled visits. For unscheduled visit, physician will decide the method based on his/her judgment. g. Bayley Scales of Infant and Toddler Development™, fourth edition (Bayley™-4)will be used for development assessment. h. Samples for immunogenicity assessment will be taken from infants born from pregnant immunogenicity subjects only. i. An infant blood draw should be preferentially obtained within 24 hours of birth if cord blood is not collected at delivery up to 72 hours post-delivery. j. Any AEs reported in infants will be categorized as unsolicited adverse events. AESI and SAE will be collected throughout the study. k. In case an infant is delivered preterm: - All infant participants do not belong to immunogenicity subsets, will undergo V2 (6 weeks after delivery) based on chronological age and V3 (6 months after delivery) based on adjusted age. - Infants belonging to immunogenicity subsets, will undergo V2 (6 weeks after delivery) based on chronological age (6 weeks after delivery), also based on chronological age. If the gap between chronological and adjusted ages exceed the window for additional visit (V3') should be scheduled at an adjusted age of 6 months. Should this additional visit (V3') be scheduled at an adjusted age of 6 months, assessment and study completion form will be postponed from V3 (6 months by chronological age) to V3' (6 months by adjusted age). If the additional visit (V3') scheduled at 6 months by adjusted age, all study procedures for V3 will be conducted.	Visit Number / Visit Weeks / Visit Window / Infant Enrollment ID Assignment* / Document APGAR Score, Gestational Age at Birth* / Gross Anomaly Check / Demographic Information / Weight / Length / Head Circumference / Medical History* / Concomitant Medications* / Physical Examination* / Vital Signs / Developmental Assessment* / Blood Samples for Immunogenicity* (Cord Blood / Venous Blood) / Safety Follow Up* / Study Completion Form a. In case of home delivery, procedures can be conducted within 7 days window. b. The participant card will be given to the parent /guardian of the infant participant at the delivery visit. c. APGAR score measured at 1, 5 and 10 minutes will be collected. d. Any medical history during fetal period (e.g. anomaly detected by ultrasonography, fetal treatment conducted). e. Concomitant medications related to AE AESI SAE will be collected. f. Full physical examinations will be performed at all scheduled visits. For unscheduled visit, an attending physician examination method based on his/her judgement. g. Bayley Scales of Infant and Toddler Development™, fourth edition (Bayley™-4) will be used for development assessment. h. Samples for immunogenicity assessment will be taken from infants born from pregnant immunogenicity subjects only. i. An infant blood draw should be preferentially obtained within 24 hours of birth if cord blood is not collected at delivery up to 7 days post-delivery. j. Any AEs reported in infants will be categorized as unsolicited adverse events. AESI and SAE will be collected throughout the study. k. In case an infant is delivered preterm. - All infant participants do not belong to immunogenicity subsets, will undergo V2 (6 weeks after delivery) based on chronological age and V3 (6 months after delivery) based on adjusted age. - Infants belonging to immunogenicity subsets, will undergo V2 (6 weeks after delivery) based on chronological age (6 weeks after delivery), also based on chronological age. If the gap between chronological and adjusted ages exceed the window for additional visit (V3') should be scheduled at an adjusted age of 6 months. Should this additional visit (V3') be scheduled at an adjusted age of 6 months, assessment and study completion form will be postponed from V3 (6 months by chronological age) to V3' (6 months by adjusted age). If the additional visit (V3') scheduled at 6 months by adjusted age, all study procedures for V3 will be conducted.	SoE for infant updated per protocol V5.0, including footnote.

CRF	61	34. Concomitant Medication(Neonates/Infants) - BV1 (Delivery), BV2 (W6), BV3 (W24), BUV Concomitant Medication(Neonates/Infants) Are there any other medications you took besides the Investigational Product during of the study? → If 'Yes', please specify the details below. → After D28 from each vaccination, concomitant medication history related to SAEs	34. Concomitant Medication(Neonates/Infants) - BV1 (Delivery), BV2 (W6), BV3 (W24), BUV Concomitant Medication(Neonates/Infants) Are there any other medications you took besides the Investigational Product during the time of the study? ○Yes ○No → If 'Yes', please specify the details below. → Concomitant medication related to AESIs/SAEs only will be recorded.	Updated description for concomitant medication(Neonates) as no vaccination is performed for infant.

(In order to avoid conflict of interest, the Secretary, CSC (being evaluator of the case) will not participate in voting.)

9. The case was placed before the CSC for consideration.

Decision: The CSC deferred the case till the decision of the Sub-Committee on SAEs.

10. The meeting of Sub-Committee is scheduled on 20th May, 2025. Recommendations will be presented before the CSC.

11. The case was placed before the CSC for consideration. The Committee decided the case as under:

Decision:

The CSC after deliberation referring to the decision of sub-committee on SAEs decided to conduct a risk-based (triggered) GCP inspection of the site and submit report with clear and candid recommendations.

AGENDA ITEM-5: MISCELLANEOUS AGENDA ITEM

CASE No. 5.1:

REVISION OF FOLLOWING GUIDELINES IN REFERENCE TO DRAP's VIRTUAL AUDIT (NOV-2024) BY W.H.O. FOR GLOBAL BENCHMARKING FOR LEVEL-III NATIONAL REGULATORY AUTHORITY. (F.NO.08-39/2021-MISC (PS)):

It is submitted that, World Health Organization conducted DRAP's virtual audit in November 2024 as per WHO-Global Benchmarking Tool for World Listed Authorities for level-III. Though the Clinical Trial Oversight Tool got the highest (92%) implantation status among other tools, the W.H.O. in its report developed a few more Institutional Development Plans for the smooth functioning of the Clinical Trial Oversight.

2. IDPs related to guidelines are mentioned as follows:

- "***Guidelines to Conduct Clinical Research in Pakistan***" (3rd revision) has been revised as per following GBT-IDPs.
  i. CT-04.05 (Format for Progress & Final Report (CSR))
  ii. CT-06.03 (Format for Progress & Final Report (CSR))
- "***Guidelines for Conduct & Reporting of Good Clinical Practice Inspections***" (3rd revision) has been revised as per following GBT-IDPs.
  i. RI-03.01 (GCP Inspectors Competency Matrix)
  ii. RI-03.02 (GCP Inspectors Job Description)
  iii. RI-04.01 (GCP Inspectors Competency Matrix)
  iv. CT-01.06 (Risk Calculation & development of Risk–Based GCP Inspection Plan)

3. In this regard, the Pharmacy Services Division started the process of revision of guidelines and got approval from the CEO-DRAP for uploading of Guidelines on official website for comments.

4. Submitted for information of the CSC and comments on the revised guidelines.

Decision:

The CSC acceded the revision of the guidelines.

CASE No. 5.2:

APPLICATION FOR RENEWAL/ EXTENSION OF DRAP APPROVAL FOR ALREADY APPROVED CLINICAL TITLE "A PHASE II, RANDOMIZED, OBSERVER-BLINDED, PLACEBO CONTROLLED TRIAL TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF HECOLIN ® IN HEALTHY PREGNANT WOMEN BETWEEN GESTATIONAL AGE 14-34 WEEKS AND NON-PREGNANT WOMEN OF 16-45 YEARS OLD". F.NO.03-35/2023-CT (PS)

The subject trial was approved by the CSC in its 41st Meeting held on 10th April, 2023 and for a period of 2years with effect from 14th April, 2023. The PI of the trial Dr M. Imran Nisar, Principal Investigator, Associate Professor & Vice Chair Research Department of Pediatrics and Child Health, The Aga Khan University, Pakistan vide letter dated 18th March, 2025 have applied for an extension in the trial duration. His request is reproduced as under: -

> *I am writing to request your approval for the extension of the clinical trial under Registration No.* CT-*0058, as titled above. The study was initially granted approval on April 14, 2023, for two years. Due to some unforeseen delays, the study initiated on May 2, 2024, and thus could not be completed within the specified timeline. To ensure its successful completion, we request an extension of DRAP approval for two years (April 2027). Kindly note that the miscellaneous fee for this request has been submitted under Challan No. 8680891406*
> *Please find detailed enrollment status & overall study progress in the attached report. To summarize, as of February 25, 2025, a total of 1223 women have been enrolled at the Clinical trials unit (CTU) at the Aga Khan University. This constitutes 51.8% of the enrollment target of 2358 women. Among the enrolled, 1087 are pregnant women and 136 are non-pregnant women.*
> *Kindly find the following documents with the application:*
> 1. *Annual Progress Report*
> 2. *Initial DRAP Approval*
> 3. *Paid Challan form*
> 4. *A composite line-listing of the Serious Adverse Events (SAEs) and Adverse Events of Special Interest (AESI) reported till February 25, 2025.*
>
> *We remain committed to ensuring compliance with* ***Good Clinical Practice (GCP)*** *and* ***DRAP guidelines.***

2. The application was enclosed with copy of paid challan No. 49758126386 submitted fee of Rs. 122,530 on 17th April, 2025, annual progress report and line listing of SAE's.

Background of the case

The PI has periodically reported SAEs including deaths and fetal anomalies including IU growth retardation. The Chairman sub-committee on SAEs on the recommendation of the Chairman CSC ordered to conduct triggered GCP inspection of the trial site which was carried out on 02.11.2024.

Report of the said inspection was presented before the CSC in it 52nd meeting held on 28th November, 2024, moreover, the PI of the trial vide his letter dated 07.11.2024 informed that the enrolment for pregnant Women Arm of the Trial is voluntary being paused.

Decision of 52nd CSC is reproduced as under: -

> *The CSC after deliberation acceded to the Triggered GCP Inspection Report of Clinical Trial titled, "A Phase II, Randomized, Observer-blinded, Placebo Controlled Trial to Evaluate the Safety and Immunogenicity of Hecolin® in Healthy Pregnant Women between Gestational Age 14-34 weeks and Non-Pregnant Women of 16-45 years old".*

3. The annual report is reproduced as under: -

Study title	**A Phase II Randomized, Observer-blinded, Placebo Controlled Trial to Evaluate the Safety and Immunogenicity of Hecolin® in Health Pregnant Women Between Gestational Age 14-34 Weeks and Non-Pregnant Women of 16-45 Years Old.**
Protocol Number	IVI_Hecolin_P001
Principal Investigator	Dr. M. Imran Nisar
Sponsor	International Vaccine Institute
Site Name	Aga Khan Hospital
DRAP Registration Number	CT-0058
Type of report	Annual Progress Report (For Renewal of Approval)
Period	May 2024- Feb 2025

Work Summary from May 15, 2024, to February 25, 2025

The study initiated in Aga Khan Hospital Karachi, Pakistan on May 2, 2024, aiming to enroll both pregnant and non-pregnant female participants. As of February 25, 2025, screening activities at the Clinical Trials Unit (CTU) at AKU have involved 1534 women. Of these, 1223 participants have been successfully enrolled, comprising 1087 pregnant women and 136 non-pregnant women. Recruitment has achieved 50% of the total target, with ongoing efforts to complete enrollment. The summary of screening and enrollment data is as below:

Table 1. Summary of screening and enrollment data

Trial activity	Total
Screenings	1534
Enrollments	1223
Screen failures	276
Early terminated	26
Consent withdrawals	16

Delivery outcomes

Of the 1087 enrolled pregnant women, 577 (53.08%) have delivered and the delivery outcomes are given below:

Table 2: Summary of birth outcomes (15-May to 25-Feb-2025)

Outcome	Total	Percentage
Total deliveries	577	53.08%
Live births*	566	98.09%
Neonatal deaths	14	2.43%
Infant deaths	4	0.69%
Stillbirths	10	1.73%
Maternal deaths**	1	0.17%
Term births	447	77.47%
Preterm births (GA <37 weeks)	130	22.53%
Low birth weight (weight <2500 g)	150	26.00%

Safety Reporting:

- **Serious adverse events (SAE):**
  - 197 SAEs have been reported for both the participant (mother) and infant participants.
  - 73 SAEs have been reported (mothers) and 124 SAEs have been recorded for infant participants.
- **Adverse events of special interest (AESI):**
  - 556 AESIs have been reported for both the participant (mother) and infant participants.
  - 240 AESIs have been reported for the participants (mothers) and 316 AESIs have been recorded for infant participants.
- **Unsolicited adverse events (Unsol AE):**
  - 537 unsol AEs have been reported for both the participant (mother) and infant participants.
  - 222 unsol AEs have been reported for the participants (mothers) and 315 unsol AEs have been recorded for infant participants.

Please note that the data included in this are based on live data which may be updated later as per query resolutions. The final, clean data may reflect different event numbers. Summary of the adverse

events reported till 25-Feb-2025 is attached as *Appendix 1.0_HEV P001_SAE-AESI line listing_Cut off 25Feb2025_AKU.*

- **Pregnancy Reports in Non-Pregnancy Arm (Arm 3)**

Pregnancies were reported in two participants enrolled in Arm 3 (non-pregnant group), and their pregnancy reporting forms have been submitted to ERC, NBC, and DRAP.

- **Participant EM3-30029-1:**
  - Enrolled in Arm 3 on September 30, 2024.
  - Received two doses of the investigational product (IP).
  - Pregnancy reported to DRAP on November 30, 2024.
- **Participant EM3-30048-1:**
  - Enrolled in Arm 3 on November 1, 2024.
  - Received the first dose of the investigational product (IP) on the same day.
  - Pregnancy reported to DRAP on November 30, 2024.

All necessary regulatory bodies have been notified, and further monitoring will be conducted as per study protocols.

Work Plan for the Upcoming Year

1. **Completion of Enrollment:**
   a. Participant enrollment is targeted for completion by **August 2025**.
2. **Safety Monitoring & Adverse Event Management:**
   a. Enrolled participants will be closely monitored to ensure safety.
   b. Any adverse **events** will be promptly identified and managed.
3. **Regular Sponsor & Study Monitoring Meetings:**
   a. Bi-weekly meetings with the sponsor (IVI) and study monitors will continue to review study progress and address any challenges.
4. **Follow-Up Visits:**
   a. **Follow-up visits** for enrolled participants and their infants will continue until **September 2026** to ensure comprehensive data collection and participant well-being.

The study remains on track, with ongoing recruitment, monitoring, and follow-up activities aligned with the planned objectives.

(In order to avoid conflict of interest, the Secretary, CSC (being evaluator of the case) will not participate in voting.)

9. The case was placed before the CSC for consideration.

Decision: The CSC after deliberation referred the case to the Sub-Committee on SAEs for detailed evaluation of the "Annual Report" and line listing of the SAEs recorded during the trial.

10. The case was placed before the Sub-CSC on SAEs for consideration. The Sub-Committee decided the case as under:

Decision of 3rd Sub-committee on SAEs:

The Sub-committee on SAEs, considering the "Annual Report" and line listing of the SAEs recorded during the trial, recommended to conduct a risk-based (triggered) GCP inspection of the site and submit report with clear and candid recommendations.

11. The case was placed before the CSC for consideration. The Committee decided the case as under:

Decision:

The CSC after deliberation referring to the decision of sub-committee on SAEs decided to conduct a risk-based (triggered) GCP inspection of the site and submit report with clear and candid recommendations.

CASE No. 5.3:

REQUEST FOR CONSIDERATION REGARDING CRO - DRK PHARMA: SITE FEE CLEARANCE ISSUE IMPACTING OPERATIONAL AND PATIENT SAFETY STANDARDS. (F.NO.08-07/2025-MISC (PS))

Application was received from Dr. Nida Hussain, CEO, Ziauddin University Clinical Trial Unit, Clifton, Karachi, dated 22nd April 2022 on the above cited subject. Application is reproduced as under:

> ***SUBJECT: Request for Consideration Regarding CRO - DRK Pharma: Site Fee Clearance Issue Impacting Operational and Patient Safety Standards***
>
> *I Dr. Nida Hussain CEO at M/s Ziauddin University Clinical Trial Unit, having Clinical Trial Site License No. CTS- 0086, would like to bring to your attention a matter of concern regarding the Contract Research Organization DRK Pharma, registered with DRAP under Registration No. CRO-0001.*
>
> *ZU-CTU previously collaborated with ORK Pharma on a clinical trial Titled "A phase III, Randomized, comparator-controlled, double-blind, Multicenter study to evaluate the immunogenicity, safety and lot to lot consistency of three lots of PIKA Rabies*
>
> - *Protocol No.: YS-002*
> - *DRAP Approval Date: March 15, 2023*
> - *DRAP Reference No.: F.No.03-36/2023-DD-CT*
> - *CT Registration No.: CT-0053*
>
> *All trial-related activities at our site have been conducted in compliance with applicable regulatory, ethical, and Good Clinical Practice (GCP) standards. The trial is now in its closing phase, and all deliverables have been completed from our end.*
>
> *However, despite repeated formal communications and follow-ups, DRK Pharma has yet to clear the Site Management Fees as per the executed Clinical Trial Agreement. This prolonged delay is not only causing significant operational challenges for our Clinical Trial Unit but also has broader implications on patient safety and standard of care.*
>
> *Clinical trial site fees are critical to ensuring the smooth operation of the study, including patient reimbursements, follow-up medical care, and the availability of necessary clinical and safety monitoring resources. Non-payment jeopardizes our ability to maintain a high standard of participant care and could undermine trust in the clinical trial ecosystem.*
>
> *We respectfully request DRAP to kindly take this matter into consideration and provide guidance or assistance in ensuring that the CRO fulfills its financial obligations to our site in accordance with the agreement and ethical standards of clinical trial conduct.*
> *We remain committed to upholding Good Clinical Practice (GCP) and DRAP guidelines and appreciate your support in maintaining a transparent and accountable research environment.*

2. The application was placed before the CSC for consideration. The Committee decided the case as under:

Decision:

The CSC considering the request of the applicant decided to seek clarification from M/s DRK Pharma Solution (CRO), Lahore, within fortnight, positively. This will be presented before the Committee in its forthcoming meeting.

END OF DOCUMENT