DRAFT MINUTES OF THE 37TH MEETING OF CSC HELD ON 06TH DECEMBER, 2022.

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37th Meeting of CSC was held on 06th December, 2022 under the Chairmanship of the Director Pharmacy Services Division in the Committee Room-II, 4th Floor, Drug Regulatory Authority of Pakistan, Islamabad.

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

Sr. No.	Name	Designation
01	**Dr. Noor Muhammad Shah**	**Chairman CSC** / Director Pharmacy Services.
02	**Ahsan Ul Haq Athar**	**Secretary,** Deputy Director-II, Pharmacy Services Division-DRAP.
03	**Dr. Mirza Tasawer Baig.**	Associate Professor in the Department of Pharmacy Practice, Faculty of Pharmacy, Ziauddin University, Karachi & Clinical Pharmacist at Dr. Ziauddin Hospital, Karachi. **(Sindh)**

3. Following members attended the meeting online through Zoom:

01	**Prof. Dr. Saeed Ahmad Khan**	Professor of Medicine Bolan Medical College Quetta presently serving as head of medicine department Jhalawan medical college Khuzdar. **(Balochistan)**
02	**Prof. Munawar Alam Ansari.**	Professor of Pharmacology, Dean Faculty of Pharmacy, Liaquat University of Medical Sciences, Jamshoro. **(Sindh)**
03	**Prof. Dr. Fazal Subhan.**	Department of Pharmacy, CECOS University of IT & Emerging Sciences, Hayatabad, Peshawar, **(Khyber Pakhtunkhwa)**.
04	**Dr. Faiza Bashir**	Nominee of Chairman, Pakistan Health Research Council, Islamabad.

4. Chairman, CSC welcomed all the members. Chairman, CSC also thanked members for their active participation. The Deputy Director, Pharmacy Services, presented the agenda as follows:

AGENDA ITEM I:

CONFIRMATION OF THE MINUTES OF THE 36TH CLINICAL STUDIES COMMITTEE MEETING.

The minutes of the 36th CSC meeting were shared with all CSC members through email on 21st November, 2022. All CSC members submitted their consent & no comments/queries were received from the members. Accordingly, decision of the meeting was communicated. Minutes are placed again for signatures of all members to satisfy legal provision.

Decision:

The members confirmed the minutes of 36th meeting of CSC which was held on 21st November, 2022. Available members also signed the minutes.

AGENDA ITEM II:

A PHASE II/III, RANDOMIZED, DOUBLE BLINDED STUDY TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF A BOOSTER DOSE OF PIKA-ADJUVANTED RECOMBINANT SARS-CoV-2 SPIKE (S) PROTEIN SUBUNIT VACCINE IN ADULTS ≥ 18 YEARS OLD WHO RECEIVED 2 OR MORE DOSES OF INACTIVATED COVID-19 VACCINE. (F. NO.03-09/2022 DD (PS).

The case is from Prof. Dr. Aamer Ikram (51401-0924270-9), Executive Director, M/s National Institute of Health, Park Road, Chak Shahzad, Islamabad, forwarded by Dr. Syed Rooh Ul Arifeen Naqvi, Project Manager, M/s DRK Pharma Solution, Lahore, dated 26th July, 2022. Wherein request has been made for approval of subject Clinical Trial, on prescribed Form-II of the Bio-Study Rules, 2017, along with a fee of Rs. 200,000/- deposited vide challan no. 36705789611, dated 20th July, 2022. The trial details are available on U.S National Trial Registry with identification number ***NCT05463419*** *(https://clinicaltrials.gov/ct2/show/NCT05463419)*.

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

i. **Sponsor:** Yisheng Biopharma (Singapore) Pte. Ltd., Singapore.

ii. **Purpose & description of trial:** The purpose of this study is to evaluate the efficacy, safety and immunogenicity of a booster dose of PIKA COVID-19 vaccine compared to the comparator inactivated COVID-19 vaccine in adults ≥ 18 years' old who received 2 or more doses of inactivated COVID-19 vaccine.

3. In phase II, a total of 300 eligible subjects will be randomly allocated in a 1:1 ratio to receive PIKA COVID-19 vaccine or the comparator inactivated COVID-19 vaccine. The ratio of the GMT of neutralizing antibody on Day 14 after the booster dose of PIKA COVID-19 vaccine group and inactivated COVID-19 vaccine group will be calculated. Based on the Phase I immunogenicity data of PIKA vaccine, the proposed Phase II sample size results in nearly 100% power in a two-sample t test of the log- transformed neutralizing antibody titers with a two-sided alpha=0.05. Among 300 subjects, at least 200 subjects will be enrolled as subset of long-term immunogenicity and 100 subjects will be enrolled as subset of early immunogenicity. Among the 100 early immunogenicity subset, the ratio of the GMT of neutralizing antibody on Day 7 after the booster dose of PIKA COVID-19 vaccine group and inactivated COVID-19 vaccine group will be calculated. Therefore, the 100 subjects randomized to the early immunogenicity subset will have additional blood sampling on Day 7. After completion of the 7-day safety observation following the immunization of all subjects in the Phase II trial, a Safety Monitoring Committee (SMC) meeting will be held to determine whether to initiate enrollment of participants in the Phase III trial. In phase III, total 9,000 eligible subjects will be randomly allocated in a 1:1 ratio to the PIKA COVID-19 vaccine group or the comparator inactivated COVID-19 vaccine group. The sample size provides an approximately 90% power to detect a protection rate of at least 65% by PIKA vaccine in a Poisson regression analysis with a one-sided alpha of 0.025. The calculations consider an interim analysis performed with 50% of the information collected using a Pocock boundary to adjust for multiplicity. A 1% infection rate in the control group and an approximately a 10% attrition rate are assumed. It is of note that while the actual background incidence rate can vary, the sample size requirement amounts to achieving an observation of 82 COVID-19 cases to ensure the statistical power under the 65% protection rate assumption. Similarly, the interim analysis will need to be conducted at when approximately 41 cases are observed to maintain the planned operating characteristics. Among total subjects, at least 6% subjects will be enrolled as subset of immunogenicity. Eligible subjects will receive a dose of investigational vaccine via intramuscular injection in deltoid muscle on Day 0. All subjects will be monitored for at least 30 minutes after injection. Solicited AEs will be recorded for 7 days. Unsolicited AEs and MAAEs will be recorded for 28 days following injection. SAEs, SUSARs, AESIs will be recorded for the entire

duration of the study. It will take about 13 months for each subject from enrollment to the last visit. Some subjects may withdraw or discontinue from the study during the study for any reason.

iii.Arms & Interventions:

Arm(s)	Intervention/treatment
Experimental: PIKA COVID-19 vaccine One dose of the experimental vaccine should be administered on Study Day 0 in the deltoid muscle	Biological: PIKA COVID-19 vaccine SARS-CoV-2 spike subunit protein, PIKA adjuvant
Active Comparator: Sinopharm inactivated Covid-19 vaccine One dose of the control vaccine should be administered on Study Day 0 in the deltoid muscle.	Biological: PIKA COVID-19 vaccine SARS-CoV-2 spike subunit protein, PIKA adjuvant

iv.Details regarding IMPs & required quantity along with justification:

A. Study Vaccine

Vaccine: PIKA COVID-19 Vaccine.
Dosage Form: Injection.
Composition: Each vaccine contains 5 µg amount S protein with fixed amount of PIKA adjuvant.
Route: Intramuscular injection into the deltoid muscle.

B. Control Vaccine:

Vaccine: Inactivated COVID-19 vaccine
Dosage Form: Injection
Composition: Each vaccine contains inactivated SARS-COV-2 virus
Route: Intramuscular injection into the deltoid muscle.

C. Quantity required:

Study Intervention	Test Drug	Comparator
Intervention Name	PIKA-Adjuvanted Recombinant SARS-CoV-2 Spike (S) Protein Subunit Vaccine (PIKA COVID- 19 vaccine).	COVID-19 vaccine (Vero cell) inactivated (single dose vial)
Dose Formulation	Vialed volume: 1.0 ml, Spike protein: 5 µg, PIKA adjuvant: 1.0 mg/ml, Polysorbate 80: 0.01%, Arginine hydrochloride: 140mM, Phosphate-buffered saline (PBS): Amount added depending on the final volume.	Vialed volume: 0.5ml 0.5ml dosage contains 6.5 µg of inactivated SARS-CoV-2 antigen.
Each Vial Contain	PIKA COVID-19 vaccine 1.0 ml	COVID-19 vaccine (Vero cell) inactivated 0. 5ml/vial
Quantity to be imported	165 for Phase II 1650 for Phase III Total: 1815	165 for Phase II 1650 for Phase III Total: 1815
Total box to be imported	5	To be procured locally from National Institute of Health (NIH)
Total subjects to be recruited in Pakistan	300 for Phase II 3000 for Phase III Total: 3300	

v. **Number of subjects to be recruited: 9300 Subjects (globally).** For Pakistan 300 for Phase-II & 3000 for Phase-III

vi. Study design & details:

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	9300 participants (Globally) Pakistan 300 for Phase-II & 3000 for Phase-III
Allocation:	Randomized
Intervention Model:	Sequential Assignment
Masking:	Triple (Participant, Care Provider, Investigator)
Masking Description:	Double Blind
Primary Purpose:	Prevention
Official Title:	A Phase II/III, Randomized, Double-blinded Study to Evaluate the Efficacy, Safety and Immunogenicity of a Booster Dose of PIKA Recombinant SARS-CoV-2 Vaccine in Adults Who Received 2 or More Doses of Inactivated Covid-19 Vaccine.
Estimated Study Start Date :	15th August, 2022
Estimated Primary Completion Date :	30th September, 2023
Estimated Study Completion Date :	31st December, 2023

4. The study carried out under the supervision of Dr. Aamer Ikram (National PI). The trial comprises of following primary objective(s);

i. Immunogenicity at Phase II Study [Time Frame: at day 14 after booster] Geometric mean titer (GMT) of neutralizing antibody against Omicron virus on D14 after the booster dose.

ii. Efficacy at Phase III Study [Time Frame: up to 360 days after booster] Incidence of first occurrence of Rt-PCR positive symptomatic illness after D14 of booster dose.

iii. Safety at Phase II and Phase III [Time Frame: up to 360 days after booster.] Incidence of AE, MAAE, SAE, SUSAR and AESI after booster dose.

5. Proposed Clinical Trial Site(s):

i. National Institute of Health (NIH), Islamabad.

ii. Al-Shifa Trust Research Center, Rawalpindi.

iii. Central Park Teaching Hospital, Lahore.

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.200000/- deposited vide challan number: 36705789611, dated 20th July, 2022.
3	Investigator Brochure (s)	IB for compound No. YS-SC2-010, Version: v2.0, dated: 16th June 2022 is attached.

		IB of comparator (COVID-19 Vaccine (Vero Cells) Inactivated) is not provided.
4	Final protocol	Attached Protocol No. YS-302 Version 1.0, dated 22nd May, 2022 * Insurance policy & its details need to be provided.
5	Informed consent and participant information sheet (Urdu to English)	Two separate ICF(s) for Phase-II & Phase-III are attached. Clarification for following need to be provided: * There is difference in translation in compensation description of Phase-III ICF. * Further details regarding insurance policy subscription is not provided.
6	List of participating countries	United Arab Emirates, Philippines & Pakistan.
7	Phase of trial.	Phase – II & Phase-III. * Application initially may be approved only for Phase-II & after submission of Phase-II results then its phase-III may be approved depending upon phase-ii results.
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.	The approximate required quantity of each vaccine will be as follows: i. PIKA COVID-19 vaccine 1.0 ml (165 for Phase II & 1650 for Phase III) ii. COVID-19 Vaccine (Vero cell) inactivated (single dose vial) (165 for Phase II & 1650 for Phase III) * It is informed that, test drug will be imported whereas comparator will be procured locally from NIH, Islamabad, procurement procedure & details regarding purchase of comparator from NIH, Islamabad need to be provided.
9	Site of the trial	i. Al-Shifa Trust Research Center, Rawalpindi. (Site is not approved for Phase-II Clinical Trials) ii. Central Park Teaching Hospital, Lahore. (Site is not approved for Phase-II Clinical Trials) iii. National Institute of Health (NIH), Islamabad. (Site is not approved for Phase-II Clinical Trials) * All proposed Clinical Trial Sites(s) are not approved for Phase-II Clinical Trials.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	National Institute of Health's IRB/ERC approval, dated 14th July, 2022, without any specified time of approval is attached. 352-357 **Note:** The composition of National Institute of Health's IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines. So, its approval for the subject trial is not in compliance to the Bio-Study Rules, 2017. Institute is advised to reconstitute &

		notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue approval.
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter no.4-87/COVID-110/22/, dated 07th July, 2022 (for a period of **Six** months). **Note:** As NIH's IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules, 2017. So, is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.
12	CV's of the Investigators	CVs of following experts are attached. **i. Prof. Dr. Aamer Ikram (PI), National Institute of Health (NIH), Islamabad. (258-322/Corr.)** **ii. Prof. Dr. Ume Sughra (Co-PI), Al-Shifa Trust Research Center, Rawalpindi. (324-339/Corr.)** **iii. Prof. Dr. Muhammad Ahmad, Central Park Teaching Hospital, Lahore. (340-349/Corr.)**
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following are attached: i. M/s Liaoning Yisheng Biopharma Co., Ltd., Shenyang China. ii. Pfizer Limited, UK. COA of following IMPs are attached: i. PIKA Recombinant COVID-19 Vaccine (CHO cell, S protein) Drug Substance, YS-SC2-010 Drug Substance. * GMP certificate of comparator's manufacturer (i.e. Beijing Institute of Biological Products Co. Ltd., China) need to be provided. ** CoPP/EUA of following need to be provided: i. PIKA Recombinant COVID-19 Vaccine (CHO cell, S protein) Drug Substance, YS-SC2-010 Drug Substance. ii. (COVID-19 Vaccine (Vero Cells) Inactivated)
14	Pre-clinical/clinical safety studies	Some articles are attached. It is informed that, Interim Analysis Report for Phase I PIKA Covid- 19 vaccine study is under preparation and will be submitted as part of the clinical trial application dossier for the applied study once available. Details regarding Phase-I need to be provided.
15	Summary of Protocol	Attached. As attached protocol is not finalized & signed so after its finalization & signature need to be submitted along with its summary.
16	Summary of Investigator Brochure	Summary of IB for comparator is not provided; **i. COVID-19 vaccine (Vero cell) inactivated**

17	Adverse Event Reporting Form	Attached.
18	No of patients to be enrolled in each center.	9300 Subjects (globally). For Pakistan 300 for Phase-II & 3000 for Phase-III. * It seems that Sponsor is conducting Phase-II only in Pakistan, clarification need to be provided that, why Phase-II will not be carried out at other two participating countries.
19	Name of Monitors & Clinical Research Associate	M/s DRK Pharma Solutions (Pvt) Ltd., Lahore. Details of monitor is attached.
20	Evidence of registration in country of origin.	**Not provided.** As IMPs are not registered, Emergency Use Authorization (EUA) Certificate for all IMPs need to be provided. Further lot/batch wise COAs of IMPs need to be provided. Which will be utilized in the trial after its approval.
21	Copy of registration letter (if registered in Pakistan)	**Not provided.** As IMPs are not registered, Emergency Use Authorization (EUA) Certificate for all IMPs need to be provided.
22	Sample of label of the investigational product / drug.	Attached but labels are not as per ICH-GCP guidelines & as the study is double blinded so commercial labels or labels with IMPs name can't be used.
22	Duration of trial	The duration of participation of each individual subject is approximately 13 months from the consent to last visit. Estimated timelines for study startup, recruitment and close out activities are 5 months. Total duration of study is **18** Months
23	Undertaking on Stamp paper	Attached.

7. After initial scrutiny following shortcomings were communicated vide this office letter F.No.03-08/2022 DD (PS) were communicated to applicant:

i. Insurance details of the study is not mentioned in protocol as required by ICH-GCP Guidelines.

ii. Details regarding sample collection, storage & transportation to bioanalytical laboratory in China is not provided as proposed sites haven't facilities required for bioanalysis of collected samples required in Phase-II.

iii. Application initially may be approved only for Phase-II & after submission of Phase-II results then its phase-III may be approved depending upon phase-ii results.

iv. Details regarding comparator, its manufacturer & process/way of procurement is not clear.

v. Anticipated cost of the project is not provided.

vi. IB & summary of comparator IMPs (COVID-19 Vaccine (Vero Cells) Inactivated) is not provided.

vii. There is difference in translation in compensation description of Phase-III ICF. Further details regarding insurance policy subscription is not provided in ICF.

viii. Application is for both Phase-II & Phase-III. It may be for Phase-II only & after submission of Phase-II results then its phase-III may be approved depending upon Phase-II results.

ix. It is informed in application that, test drug (IMPs) will be imported. Whereas, comparator will be procured locally from NIH, Islamabad. Comparator procurement procedure & details regarding purchase of comparator from NIH, Islamabad need to be provided.

x. All proposed Clinical Trial Sites(s) are not approved for Phase-II Clinical Trials.

xi. The composition of National Institute of Health's IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines. So, its IRB/ERC & NBC approval for the subject trial can't be considered. Institute is advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules, 2017 & then review the trial & issue a fresh approval. Then both IRB/ERC & NBC approval need to be provided.

xii. GMP certificate of comparator's manufacturer (i.e. Beijing Institute of Biological Products Co. Ltd., China) need to be provided.

xiii. CoPP/EUA of following need to be provided:

a. PIKA Recombinant COVID-19 Vaccine (CHO cell, S protein) Drug Substance, YS-SC2-010 Drug Substance.
b. (COVID-19 Vaccine (Vero Cells) Inactivated)

xiv. It is informed that, Interim Analysis Report for Phase-I, PIKA Covid- 19 vaccine study is under preparation and will be submitted as part of the clinical trial application dossier for the applied study once available. Details regarding Phase-I need to be provided.

xv. As per provided details regarding subject enrolment, it seems that Sponsor is conducting Phase-II CT only in Pakistan, clarification need to be provided that, why Phase-II will not be carried out at other two participating countries.

xvi. As IMPs are not registered, Emergency Use Authorization (EUA) Certificate for all IMPs need to be provided. Further lot/batch wise COAs of IMPs need to be provided. Which will be utilized in the trial after its approval.

xvii. Sample label are provided but labels are not as per ICH-GCP guidelines & as the study is double blinded so commercial labels or labels with IMPs name can't be used.

8. The CRO submitted reply on behalf of Major General Prof. Dr. Aamer Ikram, Executive Director National Institute of Health, Islamabad, in response to this office letter F.No.03-08/2022 DD (PS) dated 30th August 2022. The reply has been evaluated in tabulated as under;

S. No.	Shortcoming/ query	Reply	Remarks
1	Insurance details of the study is not mentioned in protocol as required by ICH-GCP Guidelines	Insurance details are provided in the study Informed Consent Form (ICF). As every subject shall keep one copy of signed ICF, therefore it is written in the ICF to keep the subject aware of the availability of insurance coverage in this study. Liability limit per person is PKR 2,500,000/-, quotation from insurance	As mentioned in the reply, no document regarding insurance details is attached.

		company is attached for your reference.	
2	Details regarding sample collection, storage & transportation to bioanalytical laboratory in China is not provided as proposed sites are not having facilities required for bioanalysis of collected samples required in Phase-II studies/trials.	For the bioanalysis, the collected samples (serum) will be shipped to the Q^2 Solutions Pte. Ltd., Singapore. The Material Transfer Agreement (MTA) between DRK Pharma Solutions (CRO), Yisheng Biopharma (Sponsor) and Q2 Solutions (Central Lab) is attached. The samples (serum) will be stored at the site (NIH) at the -20°C temperature and will be transported at the same temperature to the Q2 Solutions Pte. Ltd., Singapore.	As claimed in the reply, the Material Transfer Agreement (MTA) between DRK Pharma Solutions (CRO), Yisheng Biopharma (Sponsor) is not attached & no SOP as required is provided.
3	Application may initially be considered/approved only for Phase-II study & after submission of Phase-II results subsequently its phase-III trial may be applied afresh for consideration of the competent forum (depending upon phase-II study results).	Kindly provide the clinical trial approval for Phase II and III trial together, as the nature of trial is competitive recruitment globally for both the phases of the trial. Once the Phase II will be completed, we will submit the preliminary data analysis and Independent (Study Monitoring Committee) SMC recommendation letter to start the phase III of the trial globally. In the other participating countries (UAE & Philippines) the clinical trial approval is granted for both Phase II and Phase III (Attached for reference). In order to achieve the recruitment timelines at the same time as in UAE and Philippines, we request you to kindle give the collective approval of Phase II and Phase III with the condition of submitting the recommendation letter from Independent SMC and preliminary data analysis of Phase II.	It is again informed that, as per available record none of the applied site is approved for Phase-II Clinical Trials.
4	Details regarding comparator, its	COVID-19 vaccine (Vero cell) inactivated (single dose	Name of the Comparator IMPs is

	manufacturer & process/way of procurement need to be clarified.	vial) will be used as a comparator vaccine for YS-302 clinical trial which is already a marketed product by Beijing Institute of Biological Products Co. Ltd. Please find the attached CoA and EUA for the comparator vaccine. This will be procured locally from National Institute of Health (NIH) Pakistan. An agreement copy is attached for comparator procurement.	not provided. Further, agreement for comparator product, as stated in the reply is not provided. Role of NIH, Islamabad in procurement/import of Sinopharm Vaccine is not clarified. As supply of IMPs is sole responsibility of the Sponsor, so, it is again requested to provide details regarding comparator, its manufacturer & process/way of procurement & agreement between Sponsor & manufacturer of comparator.
5	Anticipated cost of the project is not provided.	The anticipated cost for the project is USD 3,689,475 mentioned in Form II.	---
6	IB & summary of comparator IMPs (COVID-19 Vaccine (Vero Cells) Inactivated) is not provided.	Investigator brochure and summary for Investigational Product is already provided. For comparator vaccine (Sinopharm), investigator brochure, EUA and CoA is attached.	Investigator's Brochure / EUA & CoA of Comparator IMPs (Sinopharm) is not provided.
7	There is difference in translation in compensation description of Phase-III ICF. Further details regarding insurance policy subscription is not provided in ICF.	The compensation in this study is described on ICF Page No. 13 under the paragraph addressing compensation for injury resulting from the study and similarly also translated in the ICF Urdu version.	---
8	Application is for phase-II & Phase-III, it may be for phase-II only & after submission of Phase-II results then its Phase-III may be approved depending upon Phase-II results.	Kindly provide the clinical trial approval for Phase II and III trial together, as the nature of trial is competitive recruitment globally for both the phases of the trial. Once the Phase II will be completed, we will submit the preliminary data analysis and Independent (Study	As per request to approve Phase-II & Phase-III, please provide legal provisions from law of the land or from any stringent regulatory Authority.

		Monitoring Committee) SMC recommendation letter to start the phase III of the trial globally. In the other participating countries (UAE & Philippines) the clinical trial approval is granted for both Phase II and Phase III (Attached for reference). In order to achieve the recruitment timelines at the same time as in UAE and Philippines, we request you to kindle give the collective approval of Phase II and Phase III with the condition of submitting the recommendation letter from Independent SMC and preliminary data analysis of Phase II	
9	It is informed in application that, test drugs IMPs will be imported, whereas comparator will be procured locally from NIH, Islamabad. Comparator procurement procedure & details regarding purchase of comparator from NIH need to be provided.	Response is same as explained in the Point No. 4 above	Please clarify that, NIH is manufacturer or importer of the comparator vaccine.
10	All proposed Clinical Trial Sites(s) are not approved for Phase-II studies/Clinical Trials.	Only (NIH) National Institute of Health Pakistan will participate in the Phase II of the trial and NIH had already applied for the clinical trial site license to DRAP on 23rd February 2022. Site inspection is awaited an acknowledgement copy is attached for your reference.	NIH, Islamabad is not approved CTS for Phase-II Clinical Trials.
11	The composition of National Institute of Health's IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines. So, its IRB/ERC & NBC approval for the subject	IRB composition of National Institute of Health (NIH) is as per ICH-GCP guidelines and bio-study rules 2017 i.e., it is composed of 5 members, one member (Imam Masjid) is non-scientific person and Dr. Najma is an independent	The composition of IRB is not as per ICH-GCP & the Bio-Study Rules, 2017.

	trial can't be considered. Institute is advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules, 2017, review the trial subsequently & issue a fresh approval. So both IRB/ERC & NBC approvals afresh need to be provided.	member and has no affiliation with NIH, she is an employee of UKHSA. The list of IRB members and their notification is attached for your reference.	
12	GMP certificate of comparator's manufacturer (i.e. Beijing Institute of Biological Products Co. Ltd., China) need to be provided.	GMP certificate of Beijing Institute of Biological Products Co. Ltd is not available with NIH, as we are procuring the comparator locally from National Institute of Health (NIH). As Sinopharm is approved by DRAP, therefore EUA, COA and IB is attached.	GMP Certificate is a mandatory documents & need to be provided as per Rule 8 (2) & Form-II of the Bio-Study Rules, 2017.
13	CoPP/EUA of following need to be provided for; PIKA Recombinant COVID-19 Vaccine (CHO cell, S protein) Drug Substance, YS-SC2-010 Drug Substance. (COVID-19 Vaccine (Vero Cells) Inactivated)	a) CoA for investigational medicinal product is already submitted in the clinical trial application. EUA is not available as it is an investigational product right now. b) For comparator, CoA and EUA are attached.	As per reply none of the document provided. CoPP/EUA has been requested, which is a legal requirement.
14	It is informed that, Interim Analysis Report for Phase-I, PIKA Covid- 19 vaccine study is under preparation and will be submitted as part of the clinical trial application dossier for the applied study once available. Details regarding Phase-I need to be provided.	Interim analysis report for Phase I data was submitted to DRAP on August 26, 2022. An acknowledgement copy is attached for your reference.	Approval of the NBC, IRBs/ERC for Phase-II/III Clinical Trial is granted without reviewing the Phase-I Data.
15	As per provided details regarding subject enrolment, it seems that sponsor is conducting Phase-II CT only in Pakistan, clarification	As the nature of trial is competitive recruitment globally, i.e. individual recruitment target for all the participating countries (Pakistan, UAE &	---

	needs to be provided that, why Phase-II will not be carried out at other two participating countries.	Philippines) is not fixed. As soon as the total recruitment of 300 participants is achieved globally, phase II will be closed.	
16	As IMPs are not registered, Emergency Use Authorization (EUA) Certificates for all IMPs need to be provided. Further lot/batch wise COAs of IMPs need to be provided, to be utilized in the trial after its approval.	Since the IP is the investigational product, therefore there is no EUA of IMP, whereas EUA for comparator is attached. Lot/batch wise COA of both IMP and Comparator is attached.	None of the claimed document is provided.
17	Sample label are provided but these are not as per ICH-GCP guidelines & as the study is double blinded so commercial labels or labels with IMPs name can't be used.	Study specific comparator label for Sinopharm is attached for your reference. As the comparator vaccine and the Investigational Product are different, therefore to make sure the blinding in this trial, there will be a dedicated un-blinding team to look after the IMP management and dispensing. Whereas the rest of the blinded staff will not have access to the IMP and will not be able to know that who receives the IMP and who is receiving the Comparator. By keeping two separate team at the site, blinding will be assured.	Double blinded Study so how & where it will be blinded. Further it is mentioned in form II that all All the quantities of the each of investigational product should be procured from one single source)

9. The DRK applicant has also submitted the reply in response to this office letter F.03-09/2022 DD (PS) dated 26th October 2022 and has attached following supporting documents.

i. Quotation slip for clinical trial liability insurance is attached.
ii. Material Transfer Agreement whereas **procedure/ SOP is required**.
iii. Vaccine supply agreement b/w Yisheng Biopharma (Singapore) Pte. Ltd and National Institute Health, Islamabad.
iv. Copy of EUA SARS-CoV-2 Vaccine (Vero cell), inactivated manufactured by M/s Beijing Institute of Biological Products China.
v. Trial (Phase II/III) Approval by FDA, Department of Health, Republic of the Philippines.
vi. Trial (Phase II/III) Approval by Ministry of Health & Prevention, UAE.

10. Dr. Syed Rooh Ul Arifeen Naqvi, Project Manager, DRK Solution, Lahore, has written a letter on behalf of Country Investigator (Prof. Dr. Aamer Ikram). He has stated that as per study protocol, the total recruitment in phase III is 9000 subjects. For Pakistan, the planned target recruitment in phase III is 3000 subject. As there are three countries i.e. UAE, Pakistan and Philippines, participating in

Phase III of this clinical trial. There shall be a competitive recruitment among these participating countries. As soon as the global target i.e. 9000 for phase III is achieved, the countries will stop the recruitment. As phase II with targeted recruitment has been completed on October 10, 2022. Therefore, as per the study protocol, we requested for phase III clinical trial. The protocol states that SMC will also provide Go/No Go recommendation whether to proceed to phase III after reviewing safety data of all subjects enrolled in phase II until 07 days' post vaccination. Copy of SMC report status "Go Recommendation to proceed with the initiation of phase III study" with SMC charter for phase II results is attached in which SMC has given the recommendation to start the phase III of this clinical trial. As SMC has given the Go Recommendation for phase III, the participating countries (UAE and Philippines) are starting the phase III recruitment in the last week of the October 2022. Therefore, we request you to kindly give us favorable opinion to stat phase III so that we can catch up the other participating countries in time. Because if we do not recruit the participant in time the other countries will keep on recruiting and complete the recruitment target as the nature of the trial is competitive recruitment.

11. The SMC (Safety Monitoring Committee) is the Internal Yisheng Biopharma Committee formed to provide proactive, aggregate and holistic evaluation of safety profile of the investigational product (IP) over the developmental lifecycle of the product, with periodic and documented review of available safety data.

12. The SMC after evaluation and discussion of the presented safety data of phase 2 study 7 days post the booster dose of PIKA COVID 19 vaccine, has concluded that there are no safety signals noted 7 days' post vaccine administration. SMC wrote that period of 7 days is very short to provide a full safety assessment and therefore the safety evaluation must be a continuing activity.

13. The SMC provided the Go recommendation to proceed with the initiation of the phase 3 study. However, there are some precautions enumerated by the SMC chair to be observed and presented in the next SMC meeting on 27th October 2022.

- It was recommended by the SMC chairman that all the safety data should be presented with complete information on the vaccination date and AE start date for correlation.
- A more comprehensive data needs to be included for all unsolicited AEs;
    - Date when the symptoms started.
    - Date of vaccination.
    - Detailed list of all symptoms experienced by the subjects.
    - Methods or test performed to confirm the diagnosis.
- A clearer presentation and calculation of the number of solicited, local and systemic AEs and unsolicited AEs experienced by the subjects. Some signs and symptoms of reported unsolicited AEs may overlap with the solicited AEs being collected.
- To inform all investigators to be more cautious of any unsolicited AEs reported with reference to cardiac and gastric complaints, e.g. GERD, chest discomfort and an ECG must be performed to rule out any cardiac condition such as carditis or myocarditis.

14. In light of above following queries/ shortcomings were communicated vide this office F.No.03-09/2022 DD (PS) dated 03.11.2022.

i. Clarification/ relevant rule under which EPI/ Government supply can be sold to sponsor/ used for trial.

ii. The composition of IRB (on approval letter) of NIH is not as per ICH-GCP & Bio-Study Rules 2017 as only four members have been participated in the meeting in which subject trial was evaluated & approval granted. Further two members are not as per NIH IRB notification dated 26th November 2022.

iii. GMP certificate is required under rule 8(2) & Form-II of Bio-Study Rules 2017 and ICH-E6 (R2) (5.13.1) guidelines.

iv. SOP for masking/ blinding of locally purchased vaccine and where it will be blinded.

v. SOP for material transfer is required.

vi. Has SMC report been reviewed by NBC/IRBs? If yes, then their comments/ approval please.

vi. Reply from Dr. Syed Rooh Ul Arifeen Naqvi, Project Manager, DRK Solution, Lahore, in response to this office letter F.No.03-09/2022 DD (PS) dated 3rd November 2022 has been received. The reply has been evaluated in tabulated as under;

S. No.	Shortcoming/ query	Reply
1	Clarification/ relevant rule under which EPI/ Government supply can be sold to sponsor/ used for trial.	As NIH possess the EUA of comparator vaccine (Sinopharm), NIH is also arranging the comparator vaccine (Sinopharm). Once trial is approved by DRAP, NIH will arrange the vaccine for trial from Federal Directorate of Immunization and followed by re-packing, relabeling, storage and logistic of comparator vaccine. Ghazala Parveen has submitted that Federal directorate of Immunization is willing to provide the required doses of Sinopharm for research purposes.
2	The composition of IRB (on approval letter) of NIH is not as per ICH-GCP & Bio-Study Rules 2017 as only four members have been participated in the meeting in which subject trial was evaluated & approval granted. Further two members are not as per NIH IRB notification dated 26th November 2021.	NIH has notified the composition of IRB dated 1stOctober, 2022 with the signatures of Prof. Dr. Aamer Ikram, HI(M) and **he is the PI of the study. Also newly notified IRB has reviewed the SMC and after deliberation agreed with the recommendation of this report.**
3	GMP certificate is required under rule 8(2) & Form-II of Bio-Study Rules 2017 and ICH-E6 (R2) (5.13.1) guidelines.	GMP certificate of M/s Liaoning Yisheng Biopharma co., Ltd issued by China Food and Drug administration is attached. **Certificate of GMP compliance of manufacturer for M/s Beijing Institute of Biological Products Co., Ltd issued by OGYEI National Institute of Pharmacy and Nutrition is attached.**
4	SOP for masking/ blinding of locally purchased vaccine and where it will be blinded.	SOP for blinding Procedure is attached.
5	SOP for material transfer is required.	Laboratory Manual and Lab Flow Chart of Q2 Solution is attached.

6	Has SMC report been reviewed by NBC/IRBs? If yes, then their comments/ approval please.	SMC report by IRBs of M/s CPTH, Al-Shifa Teaching Hospital and NIH has been reviewed and has given recommendation for recruitment of phase-III. NBC approval is also attached.

15. The case was placed before CSC in its 36th meeting held on 21st November 2022. The CSC decided the case as follows;

Dr. Zenaida on behalf of the Sponsor of the Study and representatives of CRO presented the case before CSC & replied the questions of the members of the Committee. After deliberation in the light of shortcomings observed and reply of Dr. Zenaida & representatives of the CRO, the Committee deferred the case and decided to give an opportunity to the applicant for responding to the following queries:

i. *The SMC report of Phase-II study is 07 days post the booster dose of PIKA Covid-19 Vaccine which is not sufficient regarding safety data & doesn't have interim analysis report/immunogenicity of Phase-II Clinical Trial.*
ii. *In report the SMC Chair, has shown concerns that, "all investigators to be more cautious of any un-solicited AEs reported with reference to cardiac & gastric complaints e.g. GERD, Chest Discomforts & an ECG must be performed to rule out any cardiac conditions such as carditis or myocarditis". Applicant was advised to explain that, what measures have been taken in this regard.*
iii. *The applicant could not justify the repacking, relabeling, storage & logistic of comparator vaccine.*
iv. *The blinding/masking procedure of IMPs, as presented by applicant was not satisfactory.*
v. *Applicant failed to provide GMP along with CoPP/Free Sale Certificate for comparator vaccine.*
vi. *Applicant failed to explain whether comparator vaccine being used in the trial is being studied with/ without permission of the manufacturer.*

2. The applicant informed that, there shall be competitive recruitment among participating countries. As soon as global target i.e. 9000 Subjects for the Phase-III is achieved, the countries will stop the recruitment. Keeping in view the competitive recruitment among the participating countries, the Committee decided that, an early meeting will be convened in-person or through Zoom, after receipt of reply to the queries/shortcomings.

16. The decision was communicated to PI of the study, Maj. Gen. Prof. Dr. Aamer Ikram, Executive Director, M/s National Institute of Health, Islamabad vide this office letter 16-36/2022 DD (PS) dated 25th November 2022. The reply to shortcomings/ queries has been submitted by the Dr. Syed Rooh Ul Arifeen Naqvi, Project Manager, DRK Pharma Solution, wherein he has stated that this is a competitive recruitment trial. The recruitment for phase III has been started in Philippines and UAE and recruitment will be stopped once global target i.e. 9000 subjects is achieved, as of now 2639 subject have been enrolled globally in Phase-III. The trial is very important for Pakistan due to the following reasons;

i. The PIKA protein is a new technology and trial has been started with the hope that it will have immunogenicity for a year or more after the booster dose.
ii. The manufacturer has preventive/ prophylactic rabies vaccine and we are/ will negotiate with them to bring the same in Pakistan. They are also having Flu and Hepatitis B vaccine that can be negotiated as per country requirement.
iii. The NIH have brought the previous vaccine in Pakistan e.g. PAKVAC and has the aim to bring YB vaccine technology/ repacking in Pakistan too.

iv. Trials/ transfer of technology will not only help Pakistan economically but will also help us in capacity building.

17. The following are para-wise replies to the queries raised by honorable Clinical Studies Committee in tabulated form.

Sr. No.	Shortcoming/ queries raised by CSC	Replies from Applicant
I	The SMC report of Phase-II study is 07 days post the booster dose of PIKA Covid-19 Vaccine which is not sufficient regarding safety data & doesn't have interim analysis report/ immunogenicity of Phase-II Clinical Trial.	The SMC report of phase II study 14 days post the booster dose of PIKA Covid-19 vaccine (comprising extensive safety data including overall Solicited AE's, unsolicited AE's and Summary of Medically Attended Adverse Events by severity, Summary of participants with Covid-19 infection) is attached for your kind reference. As per the latest SMC report, it was included that there are no safety signals noted 14 days post booster dose of PIKA covid-19 vaccine administration. Following are the recommendations of SMC: • The SMC recommended to continue the Phase 3 study without modification. The investigators and clinical sites must be reminded of the following: All unsolicited AEs should be closely monitored. • Any unusual findings even if there are no symptoms presented by the subject should not be taken for granted. • If there would be unusually high level of blood test like fibrinogen, chest pain or GERD, SMC must be notified immediately. CROs and sites should also be on the lookout for these events. In any case that there would be another case of hyperfibrinogenemia reported during the study, SMC will need to analyze and assess the events promptly. If this will trigger any of the pausing rules in the study, then SMC will provide the recommendation. The SMC blinded report along with the recommendation to continue the phase III study without modification is attached for your kind reference. (Attachment 1)
ii	In report the SMC Chair, has shown concerns that, "all investigators to be more cautious of any un-solicited AEs reported with reference to cardiac & gastric complaints e.g. GERD, Chest Discomforts & an ECG must be	As per the recommendations of the SMC chair, the following precautionary measures have been adopted by the sponsor and are implemented in the ongoing Phase-III trial via memorandum. The following procedures for safety assessments will be

	performed to rule out any cardiac conditions such as carditis or myocarditis". Applicant was advised to explain that, what measures have been taken in this regard.	added on Screening and D7 for subjects enrolled in Phase III: • Hematology on screening • Coagulation test on screening and Day 7 • ECG on screening and Day 7 Memorandum is attached for your kind reference. (Attachment 2).
Iii	The applicant could not justify the repacking, relabeling, storage & logistic of comparator vaccine.	There is no relabeling and repacking of the comparator vaccine. Only the computer generated randomization code will be pasted on the individual vial. As per the comparator storage requirements, it will be stored at temperature controlled warehouse (2-8°C) with multiple power backups and data loggers. Moreover, it will be transported to each clinical trial site using temperature controlled vehicles and cold boxes.
Iv	The blinding/masking procedure of IMPs, as presented by applicant was not satisfactory.	DRK is responsible to make sure that the blinding/masking of the comparator vaccine/Investigational product is followed and remained intact at each site throughout the trial. For this purpose, there shall be separate dedicated team of monitors, dispensing pharmacist and the vaccinator. The vaccine will be prepared and filled in the syringe in a separate room by the un-blinded pharmacist and inoculated by the un-blinded vaccinator. The SOP for blinding of vaccine is attached with this letter for your kind reference (Attachment 3).
v	Applicant failed to provide GMP along with CoPP/Free Sale Certificate for comparator vaccine.	The following documents are attached as required (Attachment 4): • GMP of comparator • Free Sale certificate of comparator • Comparator's Emergency use listing (EUL) of WHO
Vi	Applicant failed to explain whether comparator vaccine being used in the trial is being studied with/ without permission of the manufacturer.	There are number of approved covid-19 vaccines available in market for mass vaccination. That is why, the inactivated comparator vaccine is used as control group instead of placebo. This trial is ongoing in Philippines and UAE as well and the comparator vaccine is arranged through local health authorities. Since it is a research project and for the wellbeing of the mankind to find a better vaccine, the comparator-controlled trials are always encouraged. This trial is also publically registered on *clinicaltrial.gov* to have free access for everyone. We could not find any clause in the Bio-Study Rules 2017, ICH-GCP guidelines and any publication that prohibit the use of the marketed product to be used as comparator for any trial.

18. The applicant also wrote that Honorable CSC committee is kindly requested to have an early meeting to facilitate the approval of this trial. They have also requested to allow them import the mentioned quantity of 1650 of IMP (PIKA COVID-19 vaccine) and 540 kits of clinical trial consumables (kits for immunogenicity sampling) as well.

19. The Secretary CSC presented the case before the Committee & representatives form CRO also joined the meeting to answer queries raised by the CSC members. The Committee decided the case as follows:

Decision:

*The reply of applicant was presented before the Committee. Representative of CRO, The M/s DRK Pharma Solution Lahore (Dr. Rooh Ul Aarfeen & Mr. Talha) also appeared before the Committee for replies of the questions of the members of the Committee & clarification in the matter. The Committee after thorough deliberations on the replies of questions raised during the previous meeting & clarification of representatives of CRO, decided to grant approval of trial titled, "A PHASE II/III RANDOMIZED, DOUBLE-BLIND STUDY TO EVALUATE THE EFFICACY, SAFETY AND IMMUNOGENICITY OF A BOSTER DOSE OF PIKA-ADJUVANTED RECOMBINANT SARS-CoV-2 SPIKE (S) PROTEIN SUBUNIT VACCINE IN ADULTS ≥ 18 YEARS OLD WHO RECEIVED 2 OR MORE DOSES OF INACTIVATED COVID-19 VACCINE" for **Phase-III** as per approval of NBC and respective IRBs, to be conducted at following sites.*

i. Al-Shifa Eye Trust Research Center, Rawalpindi.
ii. Central Park Teaching Hospital, Lahore.
iii. National Institute of Health (NIH), Islamabad.

2. The CSC also acceded the request of the applicant regarding import of 1650 vial/ doses of Investigational Medicinal Products (PIKA Vaccine) and 540 Kits for immunogenicity sampling subject to issuance of NOC by concerned Assistant Director (I & E)

3. The CSC also clarified that, the applicant of the Study (Form-II), CRO & Comparator Vaccine EUA holder shall be responsible for the matters related to usage of Comparator Vaccine in the subject study.

AGENDA ITEM III:

APPLICATION FOR APPROVAL OF CLINICAL TRIAL TITLED "EFFECTIVENESS OF NOVEL APPROACHES TO RADICAL CURE WITH TAFENOQUINE AND PRIMAQUINE (EFFORT)- A RANDOMIZED CONTROLLED TRIAL IN P. VIVAX PATIENTS". FROM AGA KHAN UNIVERSITY HOSPITAL, KARACHI. F. No.03-10/2022-DD (PS)

Applicant is from Dr. M. Asim (42201-0543067-7), Professor and Consultant Parasitologist, institutional Lead for APMEN, Former Chair Hospital Ethics Committee, Department of Pathology & Microbiology, Aga Khan University, Stadium Road, Karachi, dated 28th July, 2022. Wherein request has been made for approval of subject Clinical Trial on prescribed Form-II of the Bio-Study Rules, 2017, along with a fee of Rs.200000/- deposited vide challan number: 30174303601, dated 15th July 2022. The trial is also enlisted on U.S National Trial Registry with identification number NCT04411836 *(https://clinicaltrials.gov/ct2/show/NCT04411836)* (Page 413-418/Corr.)

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

i. **Sponsor:** Menzies School of Health Research, Australia
ii. **Collaborators**:
    a. Aga Khan University Hospital, Karachi, Pakistan.

b. University of Melbourne, Australia.
c. National Centre for Parasitology, Entomology and Malaria Control, Cambodia.
d. Mahidol Oxford Tropical Medicine Research Unit, UK.
e. Ethiopian Public Health Institute, Ethiopia.
f. Universitas Sumatera Utara, Indonesia.
g. Arba Minch University, Ethiopia.

iii. **Contact information:** Kamala Thriemer, MD, MPH, PhD
0889468644
kamala.ley-thriemer@menzies.edu.au

iv. **Purpose of trial:** There have been three major advances in the tools available to tackle P. Vivax relapses recently: single dose Tafenoquine (TQ), short course high dose Primaquine (PQ) and a novel quantitative point of care G6PD test. Whilst single dose radical cure with TQ represents a major advance, there are concerns that the pivotal Phase 3 clinical trials were designed for non-inferiority to the low dose PQ regimen. There is increased evidence that in many locations, low dose PQ is inferior to a high dose PQ regimen. Now that the G6PD diagnosis can be assured and short-course high-dose PQ can be administered safely, there is a dire need to compare the safety and efficacy of these alternative treatment strategies. We propose a multicenter open label randomized controlled study to compare the effectiveness of these three key radical cure options, their safety, cost effectiveness and feasibility.
The study is designed as a prospective parallel group randomised controlled superiority effectiveness trial of patients with uncomplicated P. Vivax malaria. For the purpose of study preparation, only patients with a G6PD activity > 70oA of the adjusted male median (AMM) as determined by the Biosensor™ (SD Bioline, ROK) will be eligible for enrolment into the trial. In order to determine l0O% G6PD activity in each site, a total of 30 non-related adult males attending the health facility will be sampled, who will only be included in the pre-study to calculate the local AMM if they are negative for malaria as confirmed by microscopy, no history of fever in the receding 48 hours, no history of malaria, major injury, surgery or blood transfusion within the last 6 months. Written informed consent will be requested along with a 10µl fingerpick sample and G6PD activity will be measured in duplicate using the Biosensor. No follow up of those patients will be required.
Eligible patients who have provided written informed consent will be enrolled into the following treatment arms in a ratio of 1 :1 :1.

a) ***The control arm:*** patients are treated with schizontocidal treatment plus low dose PQ (total dose 3.5mg/kg) unsupervised over 14 days (PQ14)
b) ***The first intervention arm:*** patients are treated with schizontocidal treatment plus high dose PQ (total dose 7 mg/kg) unsupervised over 7 days (PQ7)
c) ***The second intervention arm:*** patients are treated with schizontocidal treatment plus a single dose of Tafenoquine (TQ)

v. Detailed Description:

- To assess the effectiveness of a short-course of high dose Primaquine (total dose 7mg/kg given unsupervised over 7 days) compared to the current standard low dose Primaquine regimen (total dose 3.5mg/kg given unsupervised over 14 days).
- To assess the effectiveness of Tafenoquine (single dose of 300mg) compared to the short-course high dose Primaquine regimen.
- To assess the safety of Tafenoquine compared to the high and low dose Primaquine regimens.
- To assess the cost-effectiveness and feasibility of high dose Primaquine and Tafenoquine compared to the current low dose Primaquine regimen

vi. Study design & details:

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	960 participants (Globally) as per US Trial Registry 720 participants (Globally) as per application & 240 participants in Pakistan.
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	None (Open label)
Primary Purpose:	Treatment

Official Title:	Effectiveness of Novel Approaches to Radical Cure with Tafenoquine and Primaquine - a Randomized Controlled Trial in P. Vivax Patients
Estimated Study Start Date :	25 April, 2021
Estimated Primary Completion Date :	01st June, 2022
Estimated Study Completion Date :	31st December, 2022

vii. Eligibility Criteria:

a. Inclusion Criteria
- P. Vivax peripheral parasitemia (mono-infection) as determined by microscopy.
- G6PD normal status (G6PD activity ≥ 70% of the adjusted male median as determined by the Biosensor™ (SD Biosensor, ROK))
- Fever (temperature ≥37.5ºC) or history of fever in the preceding 48 hours
- Age ≥18 years
- Written informed consent
- Living in the study area and willing to be followed for six months

b. Exclusion Criteria:
- Danger signs or symptoms of severe malaria.
- Anaemia (defined as Hb <8g/dl)
- Pregnant or lactating females
- Known hypersensitivity to any of the study drugs
- Regular use of drugs with haemolytic potential

3. Details regarding Clinical Trial Sites, PI & Co-PI in Pakistan is as follows:

A. Khidmat-e-Alam Medicine centre, Karachi, Nazimabad, Pakistan (Not approved yet)
- **i.** Principal Investigator: Asim Beg, MD.
- **ii.** Sub-Investigator: Dr. Najia Ghanchi, MD.
- **iii.** Sub-Investigator: Dr. Momin Kazi, MD.
- **iv.** Sub-Investigator: Dr. Farah Qamar, MD.

B. Thatta Civil Hospital, Thatta, Sindh, Pakistan (Not approved yet)
- **i.** Principal Investigator: Asim Beg, MD.
- **ii.** Sub-Investigator: Najia Ghanchi, MD.
- **iii.** Sub-Investigator: Momin Kazi, MD.

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached
2	Prescribed Fee	Rs.200000/- deposited vide challan number: 30174303601, dated 15th July 2022.
3	Investigator Brochure (s)	Attached **i.** Kodatef ® (Tafenoquine Succinate) 100mg Tablet (14-27/Corr.) **ii.** Primaquine 15mg Tablets (28-33/Corr.)
4	Final protocol	Attached Version 2.2, dated August, 2022 * In study objective Pakistan is not mentioned. ** Details of trial subject insurance & finance amount is not mentioned.
5	Informed consent and participant information sheet (Urdu to English)	ICF in English, Urdu & Sindhi are attached but following point need to be clarified * It is mentioned in the Informed Consent Form that, "*The study cannot compensate you or pay for life-long or long-*

		term care for study related injuries or for any long-term ill effects to your health".
6	List of participating countries	Ethiopia, Indonesia, Cambodia & 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.	The approximate required quantity of IMPs are as follows: **i.** Kodatef (Tafenoquine) 100 mg Tablets 19 boxes (16 tablets per box) **Total 304 Tablets** **ii.** Primaquine 15mg Tablets 31 boxes/bottles (250 tablets per box/bottle) **Total 7750 Tablets.** * Justification for IMPs as per number of subject & dosing need to be provided.
9	Site of the trial	a. Khidmat-e-Alam Medical center, Nazimabad, Pakistan. b. Thatta Civil Hospital, Thatta, Sindh province, Pakistan.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	AKUH IRB/ERC approval, dated 05th August, 2022 for a period of one year is attached.
11	Approval of National Bio-ethics Committee (NBC)	Approval reference letter no.4-87/COVID-111/22/123, dated 10th August, 2022 (for a period of **Six** months).
12	CV's of the Investigators	CVs of following are attached. **i.** Dr. Muhammad Asim Beg, AKUH, Karachi (National-PI) (81-110/Corr.) **ii.** Dr. Farah Naz Qamar, AKUH, Karachi (Co-PI) (11-123/Corr.) **iii.** Dr. Abdul Momin Kazi, AKUH, Karachi (Co-PI) (124-149/Corr.) **iv.** Dr. Najia Ghanchi, MD., AKUH, Karachi (Co-PI) (150-164/Corr.) ***** All above PI/Co-PI are from AKUH, Karachi, none of PI/Co-PIs are nominated from proposed CTS(s).
13	GMP certificate along with COPP & free sale certificate of the investigational product.	GMP Certificate(s) of following IMPs manufacturer(s) are attached: i. M/s The Government Pharmaceutical Organization, Thailand. ii. M/s Piramal Pharma Limited, India. CoPP/Free Sale Certificate(s) of following IMPs are attached: i. Primaquine 15mg Tablets manufactured by M/s The Government Pharmaceutical Organization, Thailand. * CoPP/Free Sale Certificate for Kodatef (Tafenoquine as succinate) 100mg Tablets manufactured by M/s Piramal Pharma Limited, India, or GMP Certificate of M/s Biocelect Pty Ltd., Australia need to be provided & it should be clarified that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the applied Clinical Trial.
14	Pre-clinical/clinical safety studies	Not applicable as both IMPs are registered & PIL are provided: **i.** Kodatef ® (Tafenoquine Succinate) 100mg Tablet (14-27/Corr.) **ii.** Primaquine 15mg Tablets (28-33/Corr.)
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Not applicable as both IMPs are registered & PIL are provided: **iii.** Kodatef ® (Tafenoquine Succinate) 100mg Tablet (14-27/Corr.)

		iv. Primaquine 15mg Tablets (28-33/Corr.)
17	Adverse Event Reporting Form	Not provided.
18	No of patients to be enrolled in each center.	960 participants (Globally) as per US Trial Registry 720 participants (Globally) as per application & 240 participants in Pakistan.
19	Name of Monitors & Clinical Research Associate	Not provided.
20	Evidence of registration in country of origin.	**Not provided.** GMP Certificate(s) of following IMPs manufacturer(s) are attached: iii. M/s The Government Pharmaceutical Organization, Thailand. iv. M/s Piramal Pharma Limited, India. CoPP/Free Sale Certificate(s) of following IMPs are attached: ii. Primaquine 15mg Tablets manufactured by M/s The Government Pharmaceutical Organization, Thailand. * CoPP/Free Sale Certificate for Kodatef (Tafenoquine as succinate) 100mg Tablets manufactured by M/s Piramal Pharma Limited, India, or GMP Certificate of M/s Biocelect Pty Ltd., Australia need to be provided & it should be clarified that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the applied Clinical Trial.
21	Copy of registration letter (if registered in Pakistan)	**Not applicable.**
22	Sample of label of the investigational product / drug.	Attached but not as per ICH-GCP Guidelines, IMPs label should contain following statement: *For Investigational Use only.*
22	Duration of trial	Individual trial duration approximately 6 months Total trial duration is estimated to 24 months.
23	Undertaking on Stamp paper	Attached.

05. After initial scrutiny following shortcomings are recorded:

i. In study objective in Pakistan are not described as mentioned for other countries in provided protocol.
ii. Details regarding trial subject(s) insurance in Pakistan is not provided.
iii. Anticipated cost of the project has not been informed.
iv. It is mentioned in the Informed Consent Form that, "*The study cannot compensate you or pay for life-long or long-term care for study related injuries or for any long-term ill effects to your health*". It needs to be clarified as ethically trial associated injuries/health issues should be covered in trial subject insurance.
v. As per U.S. trial registry there are 960 participants (Globally) for the trial. Whereas in the application 720 participants (Globally) & 240 participants will be enrolled in Pakistan. Clarification need to be provided for difference in trial subjects.
vi. Justification for IMPs quantity need to be imported for the CT as per number of subject(s), dosing & surplus quantity/retention sample, need to be provided.
vii. Following proposed CTS are not approved:
    a. Khidmat-e-Alam Medical center, Nazimabad, Pakistan.
    b. Thatta Civil Hospital, Thatta, Sindh province, Pakistan.
viii. None of PI/Co-PI are involved from proposed Clinical Trial Site(s).
ix. CoPP/Free Sale Certificate for Kodatef (Tafenoquine as succinate) 100mg Tablets manufactured by M/s Piramal Pharma Limited, India, or GMP Certificate of M/s Biocelect Pty Ltd., Australia, need to be provided & it should be clarified that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the applied Clinical Trial.

x. Sample label is attached but not as per ICH-GCP Guidelines, IMPs label should contain following statement:
    a. *For Investigational Use only.*

06. In the view of above, shortcomings communicated to applicant/PI for fulfillments on 30th August, 2022 but still response is awaited.

07. It is submitted that, the case was placed before CSC in its 35th meeting held on 13th October, 2022 & the Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of following shortcomings as per Form-II of the Bio-Study Rules, 2017:

i. *As per provided documents, composition of AKUH IRB/ERC is not as per the Bio-Study Rules, 2017 & the ICH-GCP Guidelines so its approval for the subject trial is not in compliance of the Bio-Study Rules, 2017. Institute advised to reconstitute & notify its IRB/ERC as per ICH-GCP guidelines & the Bio-Study Rules 2017 & then review the trial & issue a fresh approval.*
ii. *As IRB/ERC composition is not as per ICH-GCP guidelines & the Bio-Study Rules 2017, so is not acceptable. Fresh IRB/ERC & NBC approvals need to be provided.*
iii. *AKUH has no facility of Bioanalytical Laboratory & AKH for Women Kharadar is not licensed for Phase-II Clinical Trials.*
iv. *GMP certificate of following manufacturer issued by respective country drugs regulatory body need to be provided, further, connection & role of mentioned manufacturers need to be provided.*

    a. *Pharmaceutical Packaging Professionals Pty Ltd T/A PCI Pharma Services, 3/31 Sabre Drive, PORT MELBOURNE, VIC, 3207, Australia.*
    b. *Sun Pharmaceutical Industries Ltd., Pharma Manufacturing, Vill. Ganguwala, Paonta Sahib Distt. Sirmaur (H.P.)-India*
    c. *Akesa pty Ltd., 6/141 Flinders Lane, Melbourne VIC 3000 Australia*

v. *Details regarding Subjects to be enrolled in Australia need to be provided.*
vi. *As per Informed Consent Form, the study is not insured & subjects need to file petition for compensation. It need to be clarified & study should be insured.*
vii. *Financing & insurance details is not incorporated in trial protocol.*
viii. *Anticipated cost of the project need to be informed.*

Further, applicant is directed to provide requisite documents within 30 days positively, failing which the application is liable to be rejected.

8. Accordingly, CSC decision communicated to applicant on 14th October, 2022. Dr. Ali Faisal Saleem, Associate Professor, Vice Chair - Clinical Services, Department of Pediatrics & Child Health – MC, Director. Infectious Diseases Research Laboratory, Aga Khan University Hospital, Stadium Road, Karachi, in response to CSC decision submitted following reply, which was received on 27th October, 2022.

9. Summary of submitted reply along with attachments is as follows:

Sr.	Descriptions / Shortcomings	Reply	Remarks
01	In study objective in Pakistan is not described as mentioned for other countries in provided protocol.	This is an international multi-center trial so the study objectives are standardized for all sites.	---
02	Details regarding trial subject(s) insurance in Pakistan is not provided.	Yes, trial has insurance cover and letter is attached for reference. Insurance is renewed every year by sponsor so updated letter would be provided once renewed (Page 528-529/Corr.)	---
03	Anticipated cost of the project has not been informed.	The estimated cost of the project is $ 404,771.	---

04	It is mentioned in the Informed Consent Form that, "*The study cannot compensate you or pay for life-long or long-term care for study related injuries or for any long-term ill effects to your health*". It needs to be clarified as ethically trial associated injuries/health issues should be covered in trial subject insurance.	Recommended changes have been made to the consent forms and the clause has been deleted and submitted to the NBC and the ERC.	---
05	As per U.S. trial registry there are 960 participants (Globally) for the trial. Whereas in the application 720 participants (Globally) & 240 participants will be enrolled in Pakistan. Clarification need to be provided for difference in trial subjects.	The total number of participants is indeed 960. It was 720 before Pakistan was added. So, this information has been added to the protocol and the amended protocol has been submitted to the NBC and ERC.	---
06	Justification for IMPs quantity need to be imported for the CT as per number of subject(s), dosing & surplus quantity/retention sample, need to be provided.	The quantities have been calculated based on the dosing mentioned in the protocol i.e. the number of the tablets per arm for both the Primaquine and the Tafenoquine. The considered sample size is 80 participants each arm. It is to notify that we have calculated the dosing in accordance with the dosing of the weight more than 70 kg (mentioned in protocol) just to assure the ample quantity in hand during the trial as weight among patients is uncertain. For the Primaquine we have requested to import approximately 40% of the excess medication than the required amount as this would be required in two arms and has scheduled dosing of 7 and l4 days in both PQ7 and PQl4 arms respectively. 25% of the excess is because of the anticipated relapses and the l5% of the excess quantity is to cover the wastage of the medication from the patient's side and any unforeseeable damage to medications. In case of Tafenoquine the excess quantity is approximately 25% excess than the required quantity, quantity is less considering the fact that it requires single dose, half of that excess would be for relapses and half of it would be for the wastage from patient side.	---
07	Following proposed CTS are not approved: a. Khidmat-e-Alam Medical center, Nazimabad, Pakistan. b. Thatta Civil Hospital, Thatta, Sindh province, Pakistan.	These are not the Clinical Trial sites for the concerned Project. They will be referral centers. The Clinical Trial Site is Aga Khan University where the potential participants will be referred. The amendments regarding this have been made and the revised protocols have been shared with the ERC and NBC and approval is awaited.	Following AKUH IRB/ERC approval/ amendment are attached: **i.** Approval letter No. Nil, dated 05th August, 2022 for a period of one year is attached. **ii.** Approval letter No. Nil, dated 15th September, 2022. **iii.** Approval letter No. Nil, dated 30th September, 2022. Following NBC approval/amendment letters are attached: i. Ref: No.4-87/NBC-772/22/125, dated 10th August, 2022. (Study Approval) for a period of one year. ii. Ref: No.4-87/NBC-772/22/330, dated 13th September, 2022 (Change in Clinical Trial Sites) ii. Ref: No.4-87/NBC-772 / 22/543, dated 25th October, 2022 (Increase in sample size from 720-960 subjects).

08	None of PI/Co-PI are involved from proposed Clinical trial Site(s).	Khidmat-e-Alam und Thatta Civil Hospital are the referral centers. These centers will only refer potential subjects to Aga Khan University so, there will not be such involvement of the referral physicians hence, the CO-PI and the PI ore from main Clinical Trial Site i.e. Aga Khan University .	---
09	CoPP/Free Sale Certificate for Kodatef (Tafenoquine as succinate) 100mg Tablets manufactured by M/s Piramal Pharma Limited, India, or GMP Certificate of M/s Biocelect Pty Ltd., Australia, need to be provided & it should be clarified that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the applied Clinical Trial.	We have discussed this with Biocelect, and following justification has been provided by them: The GMP certificate lists the manufacturer and the manufacturing site - as such the clearance is issued to Piramal (not to Biocelect). They submit these GMP certificates which list the manufacturer to the TGA. These certificates will never contain Biocelect details.	Kindly clarify that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the trial. If the tablets are manufactured by M/s Biocelect Pty Ltd., Australia & imported for this trial from Australia then requirements are fulfilled. Otherwise, if the tablets are manufactured by M/s Piramal Pharma, India, then toll manufacturing agreement along with CoPP issued to M/s Piramal Pharma, India need to be provided.
10	Sample label is attached but not as per ICH-GCP Guidelines, IMPs label should contain following statement: a. *For Investigational Use only.*	The medications are labelled prior dispensing by CTU pharmacist in accordance with the ICH-GCP guidelines. The sample is attached for your reference. (Page 424/Corr.)	---

10. After evaluation following shortcoming/clarification need to be provided:

i. After evaluation clarification required that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the trial (Australia or India). If the Kodatef Tablets are manufactured by M/s Biocelect Pty Ltd., Australia & imported for from Australia then requirements are fulfilled. Otherwise, if the tablets are manufactured by M/s Piramal Pharma, India, then toll manufacturing agreement along with CoPP issued to M/s Piramal Pharma, India need to be provided.

11. Secretary CSC presented the case before CSC. Dr. Muhammad Asim (PI) also joined the meeting through Zoom, CSC members raised several queries with respect to the matter in vogue but PI failed to satisfy, since he had no convincing answer regarding the IMPs origin. The Committee decided the case as follows;

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of following shortcoming as per Form-II of the Bio-Study Rules, 2017:

i. After evaluation clarification required that, from where Kodatef (Tafenoquine as succinate) 100mg Tablets will be imported for the trial (Australia or India). If the Kodatef Tablets are manufactured by M/s Biocelect Pty Ltd., Australia & imported for from Australia then requirements are fulfilled. Otherwise, if the tablets are manufactured by M/s Piramal Pharma, India, then toll manufacturing agreement along with CoPP issued to M/s Piramal Pharma, India need to be provided.

Further, applicant was given one last opportunity to provide requisite documents within 15 days positively, failing which the application will be liable to be rejected.

12. Accordingly, CSC decision was communicated on 25th November, 2022, yet response is awaited. However, Director CTU-AKUH, Dr. Saeed Hamid contacted telephonically & requested to place again agenda before the Committee, he will join the meeting along with PI to defend the case.

13. The Secretary CSC presented the case before the Committee. Dr. M. Asim Beg, PI of the trial also joined the meeting through Zoom & responded to the queries raised by the CSC members. The Committee decided the case as follows;

Decision:

Dr. M. Asim Beg, PI of the trial joined the meeting through Zoom & clarified that, IMPs will be provided by the Sponsor & imported from Australia. He also provided CoPP for Kodatef Tablets issued by TGA, Australia.

2 *The CSC after detailed discussion, deliberation & clarification from the PI decided to approve the Phase-III Clinical Trial titled, "EFFECTIVENESS OF NOVEL APPROACHES TO RADICAL CURE WITH TAFENOQUINE AND PRIMAQUINE (EFFORT)- A RANDOMIZED CONTROLLED TRIAL IN P. VIVAX PATIENTS", under the Bio-Study Rules, 2017, to be conducted at CTU, Aga Khan University Hospital, Karachi.*

3. A total of 240 subjects will be enrolled in the study and trial duration will be 24 Months. Following quantities of IMPs will be imported for the trial:

i. *Kodatef (Tafenoquine) 100 mg Tablets 19 boxes (16 tablets per box)* ***Total 304 Tablets***
ii. *Primaquine 15mg Tablets (31 boxes/bottles of 250 tablets per box/bottle)* ***Total 7750 Tablets.***

AGENDA ITEM IV:

REQUEST FOR APPROVAL OF PHASE-I CLINICAL TRIAL TITLED, "OPEN-LABEL PILOT PHASE-I STUDY OF ANTIEPILEPTIC Z-ACID NASAL FORMULATION" TO BE CONDUCTED AT CBSCR, ICCBS, UNIVERSITY OF KARACHI, KARACHI. F. No.03-65/2021-DD (PS)

Application was received from Prof. Dr. Farzana Shaheen (CNIC-37405-0337125-2), M/s H.E.J. Research Institute of Chemistry, ICCBS-University of Karachi, Karachi, dated 14th April 2021. Wherein the request has been made for registration of the subject clinical trial. Application is on prescribed form-II along with a prescribed fee of Rs.200000/- paid vide challan number 2025702, dated 25th March 2021.

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

i. **Sponsor:** Study will be funded by TDF-HEC and ICCBS. Karachi.

ii. **Name of Investigational products**: (Z)-2-(3,5,5-trimethyl-2-cyclohexen-1-ylidene) acetic acid (Z-acid).

iii. Primary Objective of the study:

a. To establish safety, and pharmacokinetic of new antiepileptic nasal formulation based on (Z)-2- (3,5,5-trimethyl-2-cyclohexen-1-ylidene) acetic acid (Z-acid).

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

S. No.	Document	Remarks
1	Application on prescribed Form-II	Attached.
2	Prescribed processing fee	Rs.200000/- deposited vide challan no.2025702, dated 25th March 2021.
3	Investigator Brochure (s)	Attached.

		Edition/Version: 1.0, dated 18th March 2021.
4	Final protocol	Attached. TDF-03-057, Version 1.0
5	Informed consent and participant information sheet (Urdu to English)	Informed consent form in English, Urdu & Sindhi language are attached.
6	List of participating countries	Pakistan only.
7	Phase of trial.	Phase – I
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.	500gm of Z-acid is available for entire study. Z-acid is new investigational product synthesized at the ICCBS, hence no need for import of the drug.
9	Site of the trial	Center for Bioequivalence Studies and Clinical Research (CBSCR), International Center for Chemical and Biological Sciences (ICCBS), University of Karachi, Karachi. CTS-0046.
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	IRB/IEC ICCBS is attached. , University of Karachi, Karachi.
11	Approval of National Bio-ethics Committee (NBC)	Attached. Ref:No.4-87/NBC-545/21/1132 dated 11th January 2021.
12	CV's of the Investigators	CVs of following (P.I. & Co-P.Is) are attached: i. Prof. Dr. Farzana Shaheen (P.I) ii. Prof. Dr. Atta Ur Rehman iii. Prof. Dr. Iqbal Choudhry iv. Prof Shabana Usman Simjee v. Dr. Zehra Batool vi. Mr. Rukesh Maharjan vii. Prof. Dr. Raza Shah
13	GMP certificate along with COPP & free sale certificate of the investigational product.	Z-acid is new investigational product synthesized at the ICCBS fully characterized by all spectroscopic data (GCMS/NMR) and 100 % purity established stability studies are conducted and details presented in Annexure-1 (Investigator's Brochure). GC/MS and UPLC method.
14	Pre-clinical/clinical safety studies	Attached.
15	Summary of Protocol	Attached.
16	Summary of Investigator Brochure	Attached.
17	Adverse Event Reporting Form	Attached but not as per CIOMS format.

18	No of patients to be enrolled in each center.	25 Subjects.
19	Name of Monitors & Clinical Research Associate	Dr. Talha Pervaiz
20	Evidence of registration in country of origin.	Not applicable as the product is for Phase-I trial & not registered yet.
21	Copy of registration letter (if registered in Pakistan)	Not applicable as the product is for Phase-I trial & not registered yet.
22	Sample of label of the investigational product / drug.	Not provided.
22	Duration of trial	01-03 Months.
23	Undertaking on Stamp paper	Not provided.

04. After initial scrutiny following shortcomings observed:

i. GMP certificate of the IMPs manufacturer is not provided.
ii. Licence to manufacture for experimental purpose is required under chapter-II, Rule 3(v) & 21 of Schedule-G of LRA Rules 1976 is required for manufacture of IMPs.
iii. Provided adverse event reporting form is not as per CIOMS format.
iv. Sample of label of the investigational product / drug needs.
v. Undertaking on Stamp paper is not provided.

05. Accordingly, shortcomings communicated to PI on 17th June, 2022.

06. Reply from Prof. Dr. Farzana Shaheen, M/s H.E.J. Research Institute of Chemistry, ICCBS-University of Karachi, Karachi, dated 19th May 2021. Wherein the FR is in reference to this division letter even number dated 27th April 2021.

07. Applicant response for shortcomings is as follows:

S.No.	Shortcomings	Reply
01	GMP certificate of the IMPs manufacturer is not provided.	Investigational medicinal product (formulation) is an experimental product developed under TDF grant of HEC in which the SEARL company is collaborating with us. The copy of Certificate of Current GMP and License to Manufacture issued by DRAP to SEARLE COMPANY are attached.
02	Licence to manufacture for experimental purpose is required under chapter-II, Rule 3(v) & 21 of Schedule-G of LRA Rules 1976 is required for manufacture of IMPs.	-do-
03	Provided adverse event reporting form is not as per CIOMS format.	Adverse event reporting form is now provided as per CIOMS Format.
04	Sample of label of the investigational product / drug needs.	Sample of Label of the investigation product is attached.
05	Undertaking on Stamp paper is not provided.	Undertaking on Stamp paper is now provided.

08. It is submitted that applicant provided a copy of Drug Manufacturing Licence of M/s The Searle Company Limited, by way of formulation. Whereas as per rule 3 of the Drugs (Licensing, Registering and Advertising) Rules, 1976 there are five different types of licenses to manufacture drug. Rule 3 of the Drugs (Licensing, Registering and Advertising) Rules, 1976 is as follows:

> *3. Types of licences to manufacture drugs: Licences to manufacture drugs shall be of the following types, namely :--*
>
> *(i) licence to manufacture by way of basic manufacture.*
> *(ii) licence to manufacture by way of semi-basic manufacture;*
> *(iii) licence to manufacture by way of formulation;*
> *(iv) licence to manufacture by way of repacking; and*
> *(v) licence to manufacture for experimental purposes.*

09. Reply from Prof. Dr. Farzana Shaheen, M/s H.E.J. Research Institute of Chemistry, ICCBS-University of Karachi, Karachi, dated 11th October 2021. Wherein the FR is in reference to this division letter even number dated 17th June 2021.

10. Applicant response for shortcomings is as follows:

S.No.	Shortcomings	Reply
01	Dosage form of proposed Investigational Medicinal Product is not clear. Either is a solution or Nasal Spray. So, manufacturing facility requirements can't be evaluated.	Dosage form of proposed Investigational Medicinal Product is I form of solution.
02	Provided IRB approval doesn't contain same subject as mentioned in application form & NBC approval.	Revised IRB approval with same subject as mentioned in NBC approval is attached.
03	MoU between research organization & the manufacturer is not provided.	Copy of MoU is attached.

11. After evaluation of submitted reply following shortcomings need to be replied:

i. Provided licence of M/s Searle Company Limited, Karachi is "*licence to manufacture by way of basic manufacture".* Whereas, for manufacture of Investigational Medicinal Products (IMPs) for research purpose "*licence to manufacture for experimental purposes*" is required.
ii. Provided agreement is between ICCBS & HEC. Whereas, M/s Searle Company Limited, Karachi mentioned as industrial partner. There are no clear term & conditions/MoU for manufacturing of IMPs for the subject Clinical Trial.

12. Accordingly, shortcomings communicated vide letter bearing F.No.03-65/2021 DD (PS), dated 24th November, 2021 but yet response is awaited.

13. Further, it is submitted that, as applied study is a Phase-I Clinical Trial & it is suggested that, a trial specific inspection may be carried out to verify the available facilities at the proposed site & its status (primary, secondary & tertiary care facility) & its feasibility for the subject trial.

14. Moreover, qualification of PI (Ph.D. Organic Chemistry) & Co-PIs may also be evaluated for emergency handling & for provision of immediate care to trial participants

15. The Secretary CSC presented the case before the Committee. The CSC discussed the matter & decided that, the site may also be re-inspected as decided in previous CSC meeting for CBSCR-ICCBS, Karachi. Further Prof. Dr. Munawar Alam Ansari submitted a request that, due to his official

responsibilities he is unable to participate in the inspection panel, so, replace him with Dr. Mirza Tasawer Baig in panel constituted for the Site. The Committee after discussion decided the case as follows:

Decision:

The CSC after detailed discussion and deliberation decided to defer the case for fulfillment/rectification of following shortcoming as per Form-II of the Bio-Study Rules, 2017:

i. *Provided licence of M/s Searle Company Limited, Karachi is "licence to manufacture by way of basic manufacture". Whereas, for manufacture of Investigational Medicinal Products (IMPs) for research purpose "licence to manufacture for experimental purposes" is required.*
ii. *Provided agreement is between ICCBS & HEC. Whereas, M/s Searle Company Limited, Karachi mentioned as industrial partner. There are no clear term & conditions/MoU for manufacturing of IMPs for the subject Clinical Trial.*

2. The applicant is directed to provide requisite documents within 30 days positively, failing which the application is liable to be rejected.

3. Furthermore, the Committee decided to re-inspect the proposed site for verification of the facilities for Phase-I, II, III & IV Clinical Trials & its status as a Primary, Secondary or Tertiary Care Facility. The Committee constituted following expert panel for inspection of the site:

i. *Prof. Dr. Fazal Subhan.*
ii. *Dr. Saif Ur Rehman Khattak,*
iii. *Dr. Mirza Tasawer Baig.*
iv. *Dr. Ahson Siddiqui,*
v. *Shafqat Hussain Danish (Coordinator)*