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REF: *B/279/5/27/2019*

30 January 2018

The Principal Investigators
African Institute of Biomedical Science & Technology (AiBST)
Wilkins Hospital
Cnr Tongogara/Rekai Tangwena
HARARE

ATTENTION: Prof C. Masimirembwa, Dr R. Thelingwani & Ms P. Tizora

Dear All,

RE: GCP Inspection report dated 5 December 2018 for the clinical trial applications MCAZ Ref: CT165/2018, CT170/2018 & CT171/2018 & the approved Clinical trials MCAZ Ref: CT147/2017 & CT148/2017

We refer to the GCP inspection that was conducted on the 5th of December 2018 by the MCAZ inspectors. We would like to thank you for your cooperation and hospitality.

Please find attached the inspection report. You are required to comment on the inspection report and submit your proposed corrective and preventive action (CAPA) on the observations which were made during the inspection.

You are required to respond within fourteen (14) days of receipt of this letter.

Yours faithfully,

MEDICINES CONTROL AUTHORITY OF ZIMBABWE

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A.T. Takaendesa (Mrs)
for: **DIRECTOR-GENERAL**

PHARMACOVIGILANCE AND CLINICAL TRIALS DIVISION

GOOD CLINICAL PRACTICE (GCP) INSPECTION REPORT

Part 1: GENERAL INFORMATION

MCAZ Clinical Trial reference:	CT147/2017, CT148/2017, CT165/2018, CT170/2018, CT171/2018
Inspection Reference Number:	01/2018
Title of Clinical Trial:	1. Clinical validation of a CYP2B6 pharmacogenomics test and dosing algorithm in the safe and efficacious use of Efavirenz and its cost effect and benefit analysis in a public healthcare setting, MCAZ Ref: CT147/2017 2. Validation of the formation of 1-beta hydroxyl deoxycholic acid (1β-OH-DCA) as a non-invasive biomaker of CYP3a, MCAZ Ref: CT148/2017 3. A cross sectional open label single-group phase IV study to evaluate the effect of CYP2D6 genotype on the efficacy of a standard tamoxifen therapy regimen in female breast cancer patients of Black African origin in Zimbabwe, MCAZ Ref: CT165/2018 4. Pharmacokinetiics and pharmacogenetics of tamoxifen in healthy volunteers: The effect of the African specific CYP2D6*17 genotype on the plasma levels of tamoxifen and its metabolotes, MCAZ Ref: CT170/2018 5. Drug-drug interaction in the co-administration of the antiretroviral drugs and the antischistosomicide praziquantel, MCAZ Ref: CT171/2018
Name of Principal Investigator(s):	1. Professor Collen Masimirembwa (CT147/2017, CT148/2017, CT170/2018) 2. Phindile Tizora (CT165/2018)

	3. Dr Roslyn Thelingwani (CT171/2018)
Clinical Trial Site:	Chitungwiza Central Hospital, AiBST Clinical Trial Unit
Sponsor:	AiBST
Date of Contact:	5 December 2018
Names of inspectors:	Mrs A.T. Takaendesa Mr L. Chirinda Miss L. M. Mumbengegwi Mr K. T. Tamirepi

Part 2: SUMMARY

1 Scope

This was a routine inspection of the AiBST CTU to ensure general compliance to GCP requirements for the clinical trials being conducted as well as those planned.

2 Objective

The purpose of the GCP inspection was to ascertain cGCP compliance of the approved and proposed studies. Compliance with cGCP provides public assurance that the rights, safety and well-being of trial participants are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

2.1 Background

The AiBST CTU had two (2) running studies which were authorized by the MCAZ with the following titles:

2.1.1 Clinical validation of a CYP2B6 pharmacogenomics test and dosing algorithm in the safe and efficacious use of Efavirenz and its cost effect and benefit analysis in a public healthcare setting, MCAZ Ref: CT147/2017

This was a phase 4, prospective randomized, double blinded non-inferiority (with respect to efficacy) and superiority (with respect to safety) clinical study.
The objectives of the study were:
i. To establish the non-inferiority of the CYP2B6 genetic test guided dosing of efavirenz against the standard dose of 600mg/day with respect to treatment efficacy.
ii. To establish the superiority of the CYP2B6 genetic tested guided dosing of efavirenz over the standard dose of 600mg/day with respect to reduction of neuropsychiatric side effects.
The study site was Chitungwiza Central Hospital OI Clinic.

2.1.2 Validation of the formation of 1-beta hydroxyl deoxycholic acid (1β-OH-DCA) as a non-invasive biomaker of CYP3a, MCAZ Ref: CT148/2017

The study aim was to explore the use of an endogenous metabolite of deoxycholic acid, 1β- OH-DCA in determination of CYP3A activity. Justification of the study was lack of evidence of 1β- OH-

DCA as a good marker for CYP3A activity, which is involved in the majority of drug metabolism pathways and plays a major role in drug-drug interactions.
The study was a parallel drug-enzyme pharmacokinetic interaction study in healthy male volunteers, with a proposed population of 30. The study was being conducted at the AiBST Phase 1 Clinical Trial Unit, housed at Chitungwiza Central Hospital. The Study products that were used were; Itraconazole (Janssen-Cilag) 100mg per day, Fluconazole (Pfizer) 50mg , Alprazolam (Pfizer) 1mg per day, Midazolam oral, 1.5mg syrup and 1.0 mg I.V infusion

The AiBST had three studies which were pending approval:

2.1.3 A cross sectional open label single-group phase IV study to evaluate the effect of CYP2D6 genotype on the efficacy of a standard tamoxifen therapy regimen in female breast cancer patients of Black African origin in Zimbabwe, MCAZ Ref: CT165/2018

2.1.4 Pharmacokinetics and pharmacogenetics of tamoxifen in healthy volunteers: The effect of the African specific CYP2D6*17 genotype on the plasma levels of tamoxifen and its metabolites, MCAZ Ref: CT170/2018

2.1.5 Drug-drug interaction in the co-administration of the antiretroviral drugs and the antischistosomicide praziquantel, MCAZ Ref: CT171/2018

Summary

The opening meeting was held at the AiBST Clinical Trial Unit, Chitungwiza Central Hospital, where the inspectorate outlined the scope of the inspection.

The opening meeting attendance was as shown below;

Name	Designation
A.T. Takaendesa	Senior Regulatory Officer, PVCT - MCAZ (Lead Inspector)
L. Chirinda	Senior Regulatory Officer, PVCT – MCAZ
L. Mumbengegwi	Regulatory Officer, PVCT - MCAZ
K. Tamirepi	Regulatory Officer, PVCT- MCAZ
P. Tizora	CT165/2018 Principal Investigator- AiBST
B. Dzingirai	Pharmacist - AiBST
I.I. Dinnes	Research Nurse - AiBST
C. Thelingwane	Administration - AiBST
M.T. Nyatsanza	Research Nurse
G. Mabadza	CTU Support
W. Mufwambi	Researcher - AiBST
C. Mutiti	CT171/2018 co-investigator - AiBST
A.Kando	Researcher - AiBST
C. Kuyi	CT170/2018 co-investigator - AiBST

Brief introductions were made and the lead inspector then outlined the purpose and program of the inspection as follows:

Purpose

1. Pre-approval inspection for three studies, CT165, CT170 and CT171 which was going to include the following:
    i. Facilities
    ii. Personnel- GCP certification
    iii. Pharmacy plan

2. Routine inspection for two approved studies, CT147 and CT148 which was going to include the following:
    i. Procedures (SOPs)
    ii. Pharmacy Plan
    iii. Patient Confidentiality
    iv. Record Keeping
    iv. Document review

Program

1. Opening meeting
2. Document Review
3. Tour of the facility
4. Pharmacy Inspection
5. Closing meeting

Study overviews and progress reports were given by the study team and they highlighted the following concerning the studies;

Approved studies

CT147

This study was on-going, and was a polymorphism study, where fast and slow metabolisers of efavirenz would be compared. It was reported to be a non-inferiority/superiority study, and used viral load and adverse events as the main parameters for comparison. Screening began in February 2018, and participants were being recruited into the 400mg arm first. To date, 175 had been recruited, and 146 were still active, since 29 had been lost to follow up. The PI amended the protocol to add more sites in order to increase their recruitment. The added sites were Seke North Clinic, Seke South Clinic, St Mary's Clinic and Zengeza 3 Clinic.

CT148

It was reported that this study had already been completed, and 30 participants had been recruited. Approximately 2-3 participants had been lost to follow up.

Proposed studies

CT165

This will be an observational study, and no medicines will be dispensed by the study. Participants will be drawn from patients already taking Tamoxifen. Blood samples will be collected from participants every 3 months. An application had been submitted to MCAZ, and they were awaiting feedback.

CT170

This will be a Phase I, PK/PD study targeting 42 participants. 3 parallel groups will be included, each participant receiving a single dose of Tamoxifen. An application had been submitted to MCAZ, and they were awaiting feedback.

CT171

This study would involve 2 arms, with 16 participants each. In one arm, the participants would receive Praziquantel alone, and in the other arm, they would receive Praziquantel and Efavirenz/Ritonavir. An application had been submitted to MCAZ, and they were awaiting feedback.

Facilities

A tour of the AiBST CTU was conducted. The CTU has a capacity to hold 30 participants. The CTU was recently built and contained all the amenities that would allow the participants to be comfortable during overnight visits. A nurse station was also available in the observation room in the CTU to enable monitoring of participants. However, the unit was currently being utilized by the hospital as there was no running study which was admitting patients at that particular time and this is the agreement the hospital had with AiBST concerning the CTU. The research team had prepared one unit without patients for the inspection team to review and this was satisfactory.

Personnel

The study had adequate personnel to attend to the participants when they were admitted. It was reported that staff had been trained on protocol implementation for the running studies, CT147 and CT148, however there was no documentation to show this.

Pharmacy Plan

The AiBST research pharmacy was inspected to ascertain if the pharmacy was ready for use by the studies which were pending approvals. The following was observed:

i. Valid premises license displayed

ii. Air- Conditioned room with painted windows to prevent direct sunlight from entering.
iii. Cupboards for storage of study medicines
iv. Refrigerator
v. Thermometers (Digital and Mercury)
vi. Lockable room, with controlled access
vii. The pharmacy SOPs and files which contained all purchase records and import records of the study medication

The Pharmacist of record outlined the points below with regards to study medication handling;

i. The study medication was going to be stored in the cupboards. None of the medication requires refrigeration.
ii. The room will be temperature controlled by the air-conditioning unit and daily temperature readings will be recorded in the logs submitted.
iii. The study was going to be using a manual dispensing system.
iv. The Study clinicians, were responsible for all the prescribing, and the dispensing will be done by the Pharmacist of record or Backup pharmacist

Documentation reviewed

i. Regulatory File for CT147
ii. Signature log sheet
iii. Research pharmacy licence
iv. Informed Consent Forms
v. Site Master File
vi. Selected Case report Files
vii. Pharmacy Plan including relevant documentation in the pharmacy

3 Observations

The classification of the observations is intended to help classify the severity of observations noted during inspections of clinical trials. Overall, the evaluation will commensurate with the nature and extent of the deviations (i.e. severity).

Definitions

Critical: Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects and/or the quality and integrity of data. Critical observations are considered totally unacceptable.

Possible consequences: rejection of data and/or legal action and/or regulatory action required.

Remark: Observations classified as critical may include a pattern of deviations classified as major, bad quality of the data and/or absence of source documents. Fraud belongs to this group. Critical observations may result in discontinuation of the study

Major: Conditions, practices or processes that might adversely affect the rights, safety or wellbeing of the subjects and/or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles.

Possible consequences: rejection of data and/or regulatory action required.

Remark: Observations classified as major may include a pattern of deviations and/or numerous minor observations.

Minor: Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well being of the subjects and/or the quality and integrity of data.

Possible consequences: Observation classified as minor indicate the need for improvement of conditions, practices and processes.

Remark: Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

3.1 Critical

None.

3.2 Major

3.2.1 Regulatory File

i. No proof of submission or approval of amendment of additional sites i.e. Seke North, Seke South, St Mary's and Zengeza 3 clinics to MCAZ and MRCZ.

3.2.2 Informed Consent Forms

i. There was poor version control of documents as evidenced by the consent forms sampled.
   a. For participant GDES 008, there were 3 study initiation questionnaires in the file, completed on 1/8/2018, 31/8/2018 ad 28/9/2018. Some of the questionnaires had a section for entering the sex of the participant on page 3, but others did not.
   b. The study initiation questionnaires did not state the version or approval date of the document.
   c. The informed consent forms used in the study were version 1.3, whereas the approved version was 1.4

ii. Clarification is required on why the study initiation questionnaire was completed 3 times for the participants

iii. For participant GDES 004, on page 4 of the screening informed consent form, the signature of "QA/QC" does not appear on the signature master list.

iv. For participant GDES 0254, M Purisa, who signed the consent form does not appear on the signature master list.

v. For participant GDES 0254, the witness did not sign the consent form

vi. Enrolment consent forms were not available

vii. Poor control of records as evidenced by the following:
   a. For participant GDES 0254, the consent form starts on page 2. Page 1 is missing

b. For participant GDES 008, there are handwritten comments on page 1 of the screening informed consent forms *"Initiated on ART Tenolam E 400mg Batch 3059532"*, but it is not stated who entered those comments.
c. For participant GDES 0254, the handwritten comments include the date of manufacture and date of expiry, but this information was not included for GDES 008.

3.2.3 Protocol training records;

i. The training records were not available for both studies therefore there was no evidence that study staff was trained on the study protocol and implementation.

3.2.4 Case Report Files

i. Prescriptions were not included and also the brand and batch number of the medicines the participants were getting were not listed.
ii. A record of tests conducted at screening was not available.

3.3.2 Master File

i. Was not specific to any study.
ii. Generic SOPs were available, but no study specific SOPs were available.

3.3 **Minor**

3.3.1 Missing documentation (Not available at the time of inspection)

i. Documentation for CT147/2018 was not available at the time of the inspection. The team highlighted that the study data collection was finished and all the documentation has been sent to AiBST offices for data analysis.
ii. Monitoring files – no DSMB reports were available for both studies, therefore there was no evidence of monitoring of the studies.
iii. SAE log was not available at the time of the inspection.
iv. Protocol deviations file was not available at the time of the inspection.

3.3.3 Study medicines

i. For CT147/2018, a record of the brands, batch numbers and expiry dates of the medicines supplied to the participants was not available at the time of inspection.

4. Conclusion

A closing meeting was conducted where the GCP inspection findings were outlined to the AiBST staff present as highlighted under observations above. The staff acknowledged the observations, and were advised that a comprehensive GCP inspection report was to be compiled and sent to the study PI.

Those present at the closing meeting were;

Name	Designation
A.T. Takaendesa	Senior Regulatory Officer, PVCT - MCAZ (Lead Inspector)

L. Chirinda	Senior Regulatory Officer, PVCT – MCAZ
L. Mumbengegwi	Regulatory Officer, PVCT - MCAZ
K. Tamirepi	Regulatory Officer, PVCT- MCAZ
P. Tizora	CT165/2018 Principal Investigator- AiBST
B. Dzingirai	Pharmacist - AiBST
I.I. Dinnes	Research Nurse - AiBST
C. Thelingwane	Administration - AiBST
M.T. Nyatsanza	Research Nurse
G. Mabadza	CTU Support
W. Mufwambi	Researcher - AiBST
C. Mutiti	CT171/2018 co-investigator - AiBST
A.Kando	Researcher - AiBST
C. Kuyi	CT170/2018 co-investigator - AiBST

The closing meeting was led by Mr L. Chirinda and Miss L. Mumbengegwi and they highlighted the observations (listed above) which were made during the inspection. The study team was also requested to clarify on the following issues concerning CT147/2018:

i. Has the study recruited any participants who were taking the efavirenz experimental dose of 200mg?
Response: the study has not been able to recruit any participant who will take the 200mg Efavirenz dose. This may be due to competing MoHCC programs such as the test and treat program where participants will not be willing to wait for their genotyping results before they are initiated to ART.

ii. Who is writing the prescriptions for the participants in CT147/2018?
Response: The participants are in the national ART program and the hospital is writing the prescriptions and monitoring the participants.

iii. CT147/2018 is a PK study and maintaining the manufacturer of study product Efavirenz is important. How is the study maintaining the manufacturer since the participants were getting their medication from the hospital and not the study?
Response: The study team and the hospital and an arrangement of maintaining one brand of Tenofovir DF/Lamivudine/Efavirenz tablets manufactured by Mylan. Currently one batch manufactured by Mylan was reserved for the study participants.

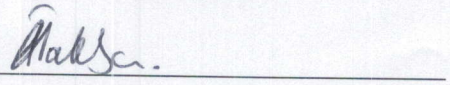
5. Recommendations to the PVCT Committee

5.1 Recommend approval of the following clinical trial applications:
- 5.1.1 CT165
- 5.1.2 CT170
- 5.1.3 CT171

5.2 A re-inspection of the following approved clinical trials, to be able to review the documentation that was unavailable at the time of inspection, and also to verify the implementation of any corrective action proposed by the studies in response to the inspection report:
- 5.2.1 CT147

5.2.2 CT148

Mrs A. T. Takaendesa

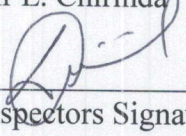


Inspectors Signature (Lead Inspector)

10/01/2019

Date

Mr L. Chirinda

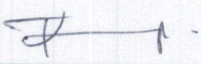


Inspectors Signature

11/01/2019

Date

Mr K. T. Tamirepi

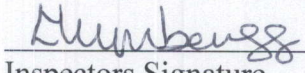


Inspectors Signature

11/01/2019

Date

Miss L. M. Mumbengegwi



Inspectors Signature

11/01/2019

Date