ANNEX A

LIST OF GCP INSPECTION OBSERVATIONS

A. PROTOCOL

4.5.1. The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement. 4.5.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted: (a) to the IRB/IEC for review and approval/favourable opinion, (b) to the sponsor for agreement and, if required, (c) to the regulatory authority(ies).

1. Critical

a. Deviations conducted by the site team that have a serious impact on the health of the subject, such as the administration of the investigational product to the subject even when prohibited concomitant therapy is involved. [ICH E6 (R2) Section 4.5.1]

b. There was a deviation from the protocol that was not communicated by the site team with the Sponsor or CRO that have a serious impact on the health of the subject and would affect the accuracy of the data. [ICH E6(R2) Section 4.5.4]

c. Deviations from the eligibility criteria (diagnostic and other than diagnostic criteria) related to the proper diagnosis of patients. [ICH E6 (R2) Section 4.5.1]

2. Major

a. There was no amendment submitted to the IRB/IEC and regulatory authorities for the implemented deviation or changes in the protocol that involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)). [ICH E6(R2) Section 4.5.4]

DRAFT

b. There was no amendment submitted to the IRB/IEC and regulatory authorities for the implemented deviation or changes in the protocol to eliminate immediate hazards to trial subjects. [ICH E6(R2) Section 4.5.4]

B. INFORMED CONSENT

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2. The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

1. Critical

a. The investigator, or a person designated by the investigator, failed to obtain and document informed consent or reconsent from a trial subject after enrollment and administration of the investigational product. [ICH E6(R2) Section 4.8.1]

2. Major

a. The written informed consent form was not signed and personally dated by the subject or by the subject's legally acceptable representative prior to commencement of clinical trial procedure. [ICH E6(R2) Section 4.8.8]

DRAFT

b. The site team failed to use the correct version of the informed consent form for most of the subjects. [ICH E6(R2) Section 4.8.2]

C. INVESTIGATIONAL PRODUCT

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see sections 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g., protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g., monitors, investigators, pharmacists, storage managers) of these determinations.

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage,

DRAFT

dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)

7.3.6 (b) Safety and Efficacy.

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

1. **Critical**
    a. Failure to maintain the required handling and storage conditions of investigational products resulting to deterioration and/or contamination. [ICH E6(R2) Section 4.6.4]
    b. Improper preparation and administration of investigational product at the investigational site/s. [ICH E6(R2) Section 7.3.6(b)]

2. **Major**
    a. The investigational product lacks a certificate of analysis to verify whether the manufactured product conforms to specification requirements. [ICH E6(R2) Section 5.13.1]
    b. The investigational product was utilized outside the approved protocol and by individuals who are not enrolled in the study (i.e. promotion and distribution or test market of investigational products). [ICH E6(R2) Section 4.6.5, 4.6.6]

DRAFT

c. No documentation or written procedures for the handling and storage of investigational product(s) for the trial and documentation of safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s). [ICH E6(R2) Section 5.14.3]

d. No documentation or monitoring records to validate storage condition of the investigational products [ICH E6 (R2) Section 5.13.2]

3. Minor

a. Records for the inventory of investigational product were not available and/or complete. [ICH E6(R2) Section 4.6.3]

b. Unsecure storage of investigational products. [ICH E6(R2) Section 5.14.3]

c. Failure to document the disposition and destruction or return of rejected or unused investigational products and/or ancillary supplies. [ICH E6 (R2) Section 5.14.3]

d. Incomplete monitoring records to validate storage conditions of the investigational products. [ICH E6 (R2) Section 5.13.2]

D. DOCUMENTATION

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.9.0 The investigator/institution should maintain adequate and accurate source documents and trial records that include all pertinent observations on each of the site's trial subjects. Source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, should not obscure the original entry, and should be explained if necessary (e.g., via an audit trail).

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

DRAFT

5.0.1 Critical Process and Data Identification During protocol development, the sponsor should identify those processes and data that are critical to ensure human subject protection and the reliability of trial results.

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

DRAFT

1. **Major**
    a. Adverse event report was not signed and graded a seriousness level by the principal investigator. [ICH E6(R2) Section 4.9.1]
    b. No applicable Standard Operating Procedures to maintain uniformity in the performance of a specific function. [ICH E6(R2) Section 5.1.1]
    c. Failure to document and compile clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. [ICH E6(R2) Section 5.0.1]
    d. The institution failed to ensure that the informed consent forms, source documents, and trial records are authentic, accurate, complete, legible, and contemporaneous. [ICH E6(R2) Section 4.9.0]
    e. The investigator failed to ensure that all persons assisting with the trial have training on GCP, protocol, standard operating procedures, and trial-related duties of the study member. [ICH E6(R2) Section 4.2.4]

2. **Minor**
    a. No proof of calibration, qualification and preventive maintenance for the equipment used for storage of investigational products. [ICH E6(R2) Section 4.6.4]

E. TRIAL MANAGEMENT

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2.6 If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated.

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following: (o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.12 If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies).

5.0.4 If the investigator/institution retains the services of any individual or party to perform trial-related duties and functions, the investigator/institution should ensure this individual or party is qualified to perform those trial-related duties and functions and should implement procedures to ensure the integrity of the trial-related duties and functions performed and any data generated. Predefined quality tolerance limits should be established, taking into consideration the medical and statistical characteristics of the variables as well as the statistical design of the trial, to identify systematic issues that can impact subject safety or reliability of trial results. Detection of deviations from the predefined quality tolerance limits should trigger an evaluation to determine if action is needed.

DRAFT

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s)

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should: (a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation).

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.18.1 Purpose. The purposes of trial monitoring are to verify that: (a) The rights and well-being of human subjects are protected. (b) The reported trial data are accurate, complete, and verifiable from source documents. (c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2 Selection and Qualifications of Monitors. (a) Monitors should be appointed by the sponsor. (b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented. (c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.21 If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

DRAFT

1. **Critical**
    a. Fraud and other scientific misconduct such as undue suspension of clinical trial operations (i.e. Sponsor-Clinical Research Organization payment issues). [Section 5.21]
    b. Use of any documents (e.g., protocol, informed consent form) without appropriate approval from FDA and/or IRB/IEC. [ICH E6 (R2) Section 4.5.1]
    c. Non-compliance with the established Standard Operating Procedures compromising the safety of the patient. [ICH E6 (R2) Section 5.1.1]
    d. Failure to report all serious adverse events (SAEs), whether expected or unexpected and laboratory abnormalities identified in the protocol as critical to safety evaluations to the sponsor and to the IRB/IEC and FDA, if applicable. [ICH E6(R2) 5.17.1]
    e. The sponsor/clinical research organization failed to ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e., validation). [ICH E6(R2) Section 5.5.3]
    f. The investigator failed to ensure that there are adequate facilities to conduct the trial properly and safely (i.e., no designated area for extraction of specimens/samples). [ICH E6(R2) Section 4.2, 8.2.12]
    g. No DOH certification for contracted third-party clinical laboratory Following A.O. 2021-0037. [Section 4.2.6]

2. **Major**
    a. Failure to notify FDA at the end of the trial or early termination within specified timelines. [ICH E6(R2) Section 4.12]
    b. Failure to submit written reports of the trial status to the FDA, IRB/IEC, and where applicable (i.e. Development Safety Update Report, annual/interim progress report). [ICH E6(R2) Section 4.10.2]
    c. Inadequate and unsecure storage of clinical trial documents and records. [ICH E6(R2) Section 4.8.10 (o)]

DRAFT

d. The investigator failed to maintain a list of appropriately qualified persons delegated with significant trial-related duties. [ICH E6(R2) Section 4.1.5]
e. The monitor has not been selected and qualified appropriately according to the purpose of a monitor. [ICH E6(R2) Section 5.18.2, 5.18.1]
f. The institution failed to secure a contract for outsourced activities which sets out arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. [ICH E6(R2) Section 4.2.6]

3. Minor

a. The sponsor/contract research organization failed to ensure that all the risks inherent in the trial are identified and controlled. [ICH E6(R2) 5.0.4]

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