RWANDA FDA
Rwanda Food and Drugs Authority

GUIDELINES FOR REVIEW AND APPROVAL OF CLINICAL TRIALS

APRIL, 2023

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GUIDELINES DEVELOPMENT HISTORY

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16/07/2021	0	First issue
03/04/2023	01	1. The reference number was changed from DIS/GDL/042 to No FDISM/PVSM/GDL/001 Rev_2 as per the current SOP on document control 2. Timelines for review during emergencies was revised as per AVAREF recommendations; 3. Components on review of safety handling were removed; 4. Criteria for accepting GMPs for imported IPs were included; 5. Statement for review by the technical committee was included; 6. Templates of the AVAREF were adopted; 7. Necessary editorial changes in line with SOP on document control were included.

FOREWORD

Rwanda Food and Drugs Authority (Rwanda FDA) is a regulatory body established by Law N° 003/2018 of 09/02/2018, specifically in article 8, paragraph 7 and 12 with a mandate to regulate and inspect clinical trials in Rwanda. Reference is made to the provisions of the technical regulation Nº FDISM/PVSM/TGR/001 Rev_2 governing the conduct of clinical trials, the Authority issues *Guidelines Nº FDISM/PVSM/GDL/008 Rev_1* for review and approval of clinical trials.

These guidelines have been developed to provide a model of review of clinical trials to ensure compliance with sound scientific aspects and regulatory requirements prior to approval and authorization by the Authority.

These guidelines were developed in reference to the existing guidelines of the World Health Organization (WHO) and the International Conference on Harmonization of Technical Requirements for Good Clinical Practices (ICH E6) and other available literature.

The Authority acknowledges all the efforts of key stakeholders who participated in the development and validation of these guidelines.

Dr. Emile BIENVENU
Director General

Digitally signed by Rwanda FDA (Director General)
Date: 2023.04.05 17:22:10 +02'00'

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ACCRONYMES AND ABBREVIATIONS

AE:	Adverse Event
API:	Active pharmaceutical Product
AVAREF:	African Vaccine Regulatory Forum
CIOMS:	Council of International Organization for Medical Science
CRO:	Contract Research Organization
CRF:	Case report form
CTA:	Clinical Trial Application
CTA-A:	Clinical Trial Application for Amendment
EUAL:	Emergency Use Assessment and Listing Procedure
GMP:	Good Manufacturing Practice
ICH:	International Conference on Harmonization
ICFs:	Informed Consent Forms
IRB:	Institutional Review Board
MTA:	Material Transfer Agreement
NDA:	New Drug Application
PI:	Principal Investigator
RNEC:	Rwanda National Research Ethics Committee
Rwanda FDA	Rwanda Food and Drugs Authority
SAE:	Serious Adverse Event
SmPC:	Summary of product characteristics
SUSARs:	Suspected Unexpected Serious Adverse
WHO:	World Health Organisation

GLOSSARY

In these guidelines:

"An applicant'' means the Sponsor or Principal Investigator. The applicant shall therefore be responsible for signing the application form.

"Authority" Means Rwanda Food and Drugs Authority or its acronym "Rwanda FDA", established by the Law Nº 003/2018 of 09/02/2018.

"Amendment" A written description of a change(s) to or formal clarification of a protocol.

"Applicable Regulatory Requirement(s)" Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

"Blinding/Masking" A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the participant(s) being unaware; and double-blinding usually refers to the participant(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

"Child" A person who is below eighteen (18) years of age or the definition of child as defined in the laws currently enforced in Rwanda.

"Case Report Form" A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each study participant.

"Clinical Trial" Any investigation in human study participants intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

"Clinical Trial Report" A written description of a trial/ study of any therapeutic, prophylactic or diagnostic agent conducted in human study participants in which the clinical and statistical description, presentations and analyses are fully integrated into a single report.

-***"Data and Safety Monitoring Board"*** An independent data monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data and the critical efficacy endpoints and to recommend to the sponsor whether to continue, modify, or stop a trial.

"Documentation" All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

"Essential Documents" Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

"Ethical Clearance" An authorization to conduct a clinical trial issued by the Rwanda National Research Ethics Committee (RNEC) or Institutional Review Boards (IRB) based on ethical issues related to trials involving human participants in Rwanda.

"Good Clinical Practice" A standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials that provide assurance that the data and reported results are credible and accurate and that the rights, integrity, and confidentiality of trial/study participants are protected.

"Good Manufacturing Practice (GMP)" The part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to quality standards appropriate to their intended use and as required by the marketing authorization.

"Impartial witness" A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the participant or the participant's legally acceptable representative cannot read, and who reads the Informed Consent Form and any other written information supplied to the participant.

"Informed Consent" A process by which a study participant voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the study participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

''Investigational Product" A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

"Investigator" A physician, dentist or other qualified person who conducts a clinical trial at a trial site. See also Sub-investigator.

"Investigator's Brochure" A compilation of the clinical and non-clinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human study participants.

"Legal representative" The name given to describe the executor, administrator or the person who looks after another person's affairs.

"Materials Transfer Agreement" An MTA is a written contract that governs the transfer of tangible research materials or biological samples between parties.

"Multi-centre Trial" A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

"Phase I trials" These are first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamic profile of the active ingredient in human.

"Phase II trials" These trials are performed in a limited number of study participants and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.

"Phase III trials" Trials in larger (and possibly varied) patient groups with the purpose of determining the short and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant investigation medicinal product interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

"Phase IV studies" Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standards as applied in pre-marketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

"Placebo" An inactive substance or sham form of a therapy administered as a control in testing experimentally or clinically the efficacy of a biologically active preparation or procedure.

"Pre-clinical Studies" Biomedical studies not performed on human study participants.

"Principal Investigator" A person responsible for the conduct of the clinical trial at a trial site who is a physician, dentist or other qualified person, resident in Rwanda and a member of good standing of a professional body. If a trial is conducted by a team of individuals at a trial site, the principal investigator is the responsible leader of the team. See also Sub-investigator.

"Protocol" A document that describes the objective(s), design, methodology, statistical considerations and organization of a trial. The protocol usually also gives the background and rationale for the trial but these could be provided in other protocol referenced documents.

"Protocol Amendment" A written description of change(s) to or formal clarification of a protocol.

"Randomization" The process of assigning trial study participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

"Source Data" All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

"Sponsor" An individual, company, institution or organization which takes responsibility for the initiation, management and/or financing of a clinical trial.

"Standard Operating Procedures (SOP)" Detailed written instructions to achieve uniformity of the performance of a specific function.

"***Substantial amendment***": means change to the terms of the protocol or any other trial supporting documentation that is likely to have significant impact and affect the safety and integrity of trial participants, the scientific value of the research, the conduct or management of the research, and the quality or safety of any investigational medicinal product used in research.

"Trial Site" The location(s) where trial-related activities are actually conducted.

1.0. INTRODUCTION

Clinical trials are planned scientific investigations conducted on humans and animals to gather information on safety and efficacy of medical products and health technologies. Such experiments involve the administration of investigational products in patients, healthy volunteers or animal species to generate data that can later be used for marketing authorization of a product.

These guidelines highlight the clinical trial review process of submitted clinical trial data to be submitted to the Authority for further authorization to conduct clinical trials in Rwanda. Good Clinical Practice (GCP) principles and other ethical considerations with the aim of ensuring the safety and protection of trial participants in Rwanda.

2.0. SCOPE

These guidelines apply to the review of all scientific aspects and regulatory requirements for initial clinical trial application, additional data if applicable, amendments, clinical trial reports including progress, close out and safety reports.

These guidelines cover the review of Clinical Trial Application (CTA) of both unregistered or registered investigational products which include pharmaceutical products, vaccines and other biological products, herbal medicines, cosmetics, medical devices and in vitro diagnostics with new intended uses.

3.0. REVIEW OF CLINICAL TRIAL APPLICATIONS

The Clinical Trial Applications (CTAs) and Clinical Trial Application amendments (CTAAs submitted to the authority are not considered valid until they have been screened for completeness. All applications for clinical conduct in Rwanda shall undergo screening and full assessment with exception of applications submitted using reliance pathways which may be waived from full assessment. In this case, the review process shall focus on regulatory requirements, review reports and decisions from other regulatory Authorities or joint review.

3.1 Screening of Clinical Trial applications

On receipt of Clinical Trial Application (CTA) or Clinical Trial Applications for amendment (CTA-A), the Authority shall assign the reference number to the application which will be communicated with applicant for future correspondences.

The application shall then be screened for completeness and compliance with the regulatory requirements **within ten (10) working days** from the submission date.

During the screening of CTA/CTAA, the Authority shall record all administrative information related to the application using screening template **(ANNEX-I)** and a screening report is developed.

The Clinical Trial Application shall pass the screening stage and be accepted for review if more than 70% of the applicable required documents are provided. This shall include but not be limited to the signed, dated application letter and forms, duly signed protocol, updated IB, proof of payment of applicable fees, declarations and agreement between the sponsor and principal investigator.

In case the applicant has provided incomplete information after screening, the Authority communicates in writing and request missing regulatory requirements.

The applicant submits missing requirements in writing to the Authority within **fifteen (15) working days** unless she/he requests for extension before deadline. Incomplete CTAs will be subjected to resubmission.

3.2 Review of Clinical Trial Applications

The accepted CTAs are subjected to the full review of protocol and its supplementary documents and investigational product dossier in order to assess the quality of the investigational product to ensure that it does not endanger the safety and well-being of clinical trial participants or other persons.

In addition, the Authority undertakes the detailed review of non-clinical data, Chemistry, Manufacturing and Control (CMC) of investigational product(s) using the review template as per **ANNEX-II.** The clinical trial application is subjected to the first and second reviews to increase transparency and quality assurance.

The review of clinical trial applications is undertaken using the same set of criteria regardless of the applicant. The review prioritization follows the first-in first-out rule (FIFO), except for clinical trials that are conducted in public health emergencies such as disease outbreaks, which may be exempted from screening and considered for expedited review.

The CTA/CTAA is reviewed by two different reviewers to ensure transparency and ensure review of safety, efficacy and quality of investigational products. The full review report will be developed using appropriate review templates as per **ANNEX-II or ANNEX VII**. Generally, the initial review of CTAs and CTA-As may result in queries or additional information that needs to be addressed by the applicant. In this situation a communication documenting all deficiencies in the application will be issued to the applicant.

3.3 Timelines for review of Clinical Trial Applications

The routine review of new clinical trial application does not exceed sixty (60) working days. In addition, the Authority may expedite or fast track the review process and approve a clinical trial application within thirty (30) working days according to the circumstances specified in the relevant guidelines.

In the event of public health emergencies, the clinical trial review process shall be conducted and provide approval of clinical trial application in 10 working days for products already registered for other indications and 15 working days for novel products.

The clinical trial application response to queries or clarifications from the applicant shall not exceed thirty (30) working days unless she/he requests for extension in writing before deadline.

These timelines shall not include the time taken by the applicant to respond to any request for additional information or clarification from the Authority. A stop-clock mechanism shall thus apply each time the Authority requests for additional information. This will help to monitor timelines for each application from the date application to the final approval.

The internal tracking system and a standards operating procedure shall be put in place to monitor compliance with above prescribed timelines for review and approval of clinical trial applications.

3.4 Types of clinical trial reviews

CTAs and CTA-As submitted to the Authority may be subjected to any of the four (4) types of reviews depending on the applicable criteria. After review, the Authority will communicate a list of queries or request for clarifications (if any) to the applicant.

3.4.1 Routine review of Clinical Trial Applications

The routine review of CTA or CTA-As is conducted by the staff within the Authority according to the established procedures and timelines.

3.4.2 Non-routine reviews of clinical trial application

The non-routine review process is a pathway for accelerating the review and approval of clinical trial application by using reliance, fast-track or expedited decision-making (e.g., receipt, screening, evaluation, review, and authorization) under certain circumstances (e.g., public health emergencies).

a) Expert Reviews

The expert reviews of Clinical trials apply when the Authority hires/invites the external reviewers following to the internal procedures depending on the complexity of clinical trial applications that require special expertise. The experts will sign a confidentiality agreement with the Authority to ensure the protection of the clinical trial information.

b) Joint Reviews

The joint reviews of Clinical Trial Applications are carried out jointly by the Authority with other relevant regulatory bodies at national, regional or international level. The applications are reviewed by experts from each participating regulatory body and the coordination is done by a designated regulatory authority. Therefore, a regulatory decision will be taken at national level once all the requirements are fulfilled.

c) Reliance during review

In case the Authority has received the clinical trial application for the protocol that has been approved by other competent regulatory authorities (ies), regional and/or international bodies, the Authority may rely on review report or valid approval and consider the review of the country specific requirements for avoiding duplication of efforts or waste of resources. The authority reserves rights to request any additional information to ensure the safety and well-being of trial participant is protected.

d) Expedited Reviews

In case of public health emergencies, the Authority may expedite the review of clinical trials for medical products aiming at preventing or treating life-threatening diseases where there is no alternative therapy. In addition, this review can apply to products listed by WHO Emergency Use Assessment and Listing (EUAL) Procedure and African Vaccine Regulatory Forum (AVAREF) readiness plan.

The review of the application for compassionate use of unauthorized investigational products shall be based on the requirements set out in latest version of AVAREF Guidance and Considerations on Compassionate Use Access.

3.5 Review of additional data & updates on clinical Applications

The sponsor or principal investigator is responsible for preparing responses to queries raised by the Authority during the review process of CTAs or CTA-As. Any new information available for the investigational product such as adverse effects, updates to the Investigator Brochure, changes in formulation or manufacturer for the active ingredients or finished products shall be notified to the Authority.

Rwanda FDA reviews the query responses/clarifications provided and if the information is satisfactory, the CTAs or CTA-As approval process are initiated. If the applicant provides non - satisfactory query responses for two successive times for the same requested information, the application shall be rejected.

3.6 Review of quality, non-clinical and clinical data

The Authority reviews quality, non-clinical and clinical data submitted to support clinical trial application. Reviewers shall pay attention on potential safety issues which may influence eventual clinical application of the investigational products.

3.6.1 Quality Review of investigational product (s)

The Authority reviews the quality part of the investigational products including placebo to ensure that the Chemistry, Manufacturing and Control (CMC) is consistently followed from active substance to finished products.
The reviewers shall verify the validity and authenticity of GMP certificate or confirmation of GMP compliance or GMP inspection report issued, by other regulatory authorities. In order to accept the GMP compliance, the Authority may rely on valid and authentic GMP certificate, confirmation or GMP inspection report issued by:

a) Stringent Regulatory Authorities/WHO listed authorities;

b) Competent Authority of countries that are standing PIC/s members;

c) World Health Organization (WHO) prequalification program;

d) Authorities operating at least at maturity level 3(ML3);

e) Competent Authority that has a recognition agreement with the Authority;

f) EAC Joint GMP inspection procedure.

In case the investigational product is manufactured in a country whose GMP control system is not recognized by the Authority, but the clinical trial has been authorized by one of the stated bodies a, b, c, d, e, and f, the decision from that body may be considered.

The information related to investigational product quality will be reviewed using a template as per **ANNEX-V** Template for Investigational Product Quality Review quality assessment template adopted from latest version of the AVAREF tools.

3.6.2 Review of non-clinical data

The review of non-clinical data will be performed focusing on the new information. A non-clinical overview on the pharmacology, pharmacokinetics, toxicology and other considerations such as Good Laboratory Practices.

The reviewer will ensure that non-clinical aspects of the SmPC are in line with the SmPC of the reference product. In addition, the reviewer (s) will provide the conclusion by using one of the following two options:

a) Pharmacodynamic, pharmacokinetic and toxicological properties of investigational products <ACTIVE SUBSTANCE> are well known. As <ACTIVE SUBSTANCE> is a widely used, well-known active substance, the applicant has provided additional studies and further studies are not required. Overview based on literature review is, thus, appropriate.

b) The reviewer(s) considers that the non-clinical overview on pre-clinical pharmacology, pharmacokinetics and toxicology is not adequate.

If the second option is chosen, the reviewer shall provide a detailed description of the missing information and its impact. This should then be translated into the draft list of questions.
The review of non-clinical data shall be made using the template for review of non-clinical data as per **ANNEX-VI** adopted from the latest version of the AVAREF tools.

3.6.3 Review of Clinical Data

During the review of clinical trial applications, the Authority shall raise any concerns about compliance with GCP or related regulatory and ethical requirements (data accuracy or protocol compliance and compliance with ethical aspects) using the template for review of clinical trial. The following will be taken into consideration where applicable:

a) Product Development Rationale

b) Overview of Biopharmaceutics (If applicable)

c) Overview of Clinical Pharmacology

d) Overview of Efficacy (If applicable)

e) Overview of Safety

f) Benefits and Risks Conclusions

3.7 Statistical Review of Clinical trial application

The Authority reviews the type of design (controlled, uncontrolled), randomization blinding, sample size determination, trial power and level of significance.

The primary and secondary variables ('target' variable, primary endpoint) will be reviewed to ensure that the proposed variable are capable of providing the most clinically relevant and convincing evidence directly related to the primary objective of the trial. The selection of the primary variable should reflect the accepted norms and standards in the relevant field of research

3.8 General review report for Clinical Trial Applications

The first and second reviewers of CTAs will generate a review report which shall include administrative and scientific details as well as other relevant information on the different sections of the protocol. In the event that there are no outstanding queries, the report will be presented and

discussed during the Clinical Trial Technical Committee (CTTC) to make a recommendation for final regulatory decision.

4.0. REVIEW OF AMENDMENTS AND RENEWAL OF CLINICAL TRIAL

The Authority shall review the substantial amendment and renewal applications for approval or rejection. In the event that these applications meet regulatory requirements, the Authority shall issue new certificates. The review shall depend on requirements for amendments or renewals as set out in the guidelines for Clinical Trial Applications in Rwanda.

The Authority shall review and approve any amendments before being implemented unless it is an urgent safety measure for trial participants. The urgent amendment shall be notified within 15 days for approval to the Authority thereafter. The list of amendments and necessary required documents prior to the approval of the amendment are detailed in the Guidelines on Clinical Trial Applications in Rwanda. The Authority will compare the new change to the previously submitted information in the protocol. The Authority reviews the amended part of the protocol and its supplementary document using the template for review of amendments as per **ANNEX-VII.**

The Authority shall review the renewal application against the requirements of renewal as stipulated in the guidelines of CTA, but also taking into account absence of harm to the trial participants in concordance with progress report and the approved protocol.

5.0. CLINICAL TRIAL APPROVAL PROCESS

Upon successful review and approval of a clinical trial application, the Authority issues a Clinical Trial Approval Certificate (CTAC) with specific number and conditions on the attachment as per the template of the CTAC is attached as **ANNEX-III.** The CTAC will have the following information: protocol title, protocol number and version if applicable, name (s) of investigational product (s) including placebo, name (s) of investigator(s), name (s) of sponsor (s), name (s) of trial sites, name of Contract Research Organization (CRO) if applicable, date of issuance and expiration date, name and signature of the Director General of the Authority.

For renewal, the Authority issues approval certificate of renewal with new validity and keep the reference number and name of the initial CTAC. In the case of amendment, the Authority shall keep the same CTAC and notify in writing the sponsor/PI.

When the sponsor/PI has not initiated the clinical trial after approval, he/she is required to communicate in writing within three (3) months. Failure to abide by the aforementioned compliance shall result to temporal CTAC suspension by the Authority until its expiration unless the sponsor/PI requests for reinstatement.

5.1 Clinical trial registration

The Authority will establish, maintain and publish of a register or database of approved, rejected clinical trial applications. The information required for register of clinical trials will include the following:

a) Application reference number

b) Protocol title

c) Sponsor

d) Principal investigator

e) Investigational product (s) name and category

f) Clinical trial site

g) Clinical Trial Phase

h) Targeted number of trial participant

i) Clinical trial duration

j) Status of the trial

k) Certificate number and validity

5.2 Publication and maintenance of clinical trial register

The Authority ensures that the register has relevant information on approved, rejected and summary of evaluation report of clinical trial applications. The outcomes of completed trials, a list and respective reasons of suspended and/or terminated clinical trials will be published and updated on monthly basis.

6.0. POST TRIAL PROTOCOL REVIEW

The authority shall review the post-trial access protocol of completed clinical trials to ensure equitable access of the treatment for the safety and welfare of trial participants until the product is commercially available. Upon satisfactory information, the Authority shall issue a notification letter for Post-Trial Access. The decision to grant post-trial access will depend on the participant's medical need, including the availability of alternative therapies and review of what is known about the benefits and risks of the investigational product. The Authority may consider granting post-trial access even when the trial was discontinued or had negative outcomes, as long as the trial was not stopped for major safety issues. The criteria include but are not limited to the following:

a) participant must have a serious or life-threatening condition

b) the treating physician and/or investigator has determined that post-trial access is the best medical option for the patient;

c) investigational product must not already be approved/authorized in that indication;

d) the participant must have been a part of the trial in which the experimental product was administered;

e) the administration of the product must have resulted in clinical benefit to the individual based on the investigator's assessment of the participant's response to the intervention and what is known about the risks of using the investigational product at the time of the decision;

f) Sponsor must accept and have an adequate supply of experimental products.

ENDORSEMENT OF TE GUIDELINES

	Author	**Authorized by**	**Checked by**	**Approved by**
Title	DM/ Pharmacovigilance & Food Safety Monitoring	HoD/ Food & Drugs Inspections & Safety Monitoring	Quality Assurance Analyst	Director General
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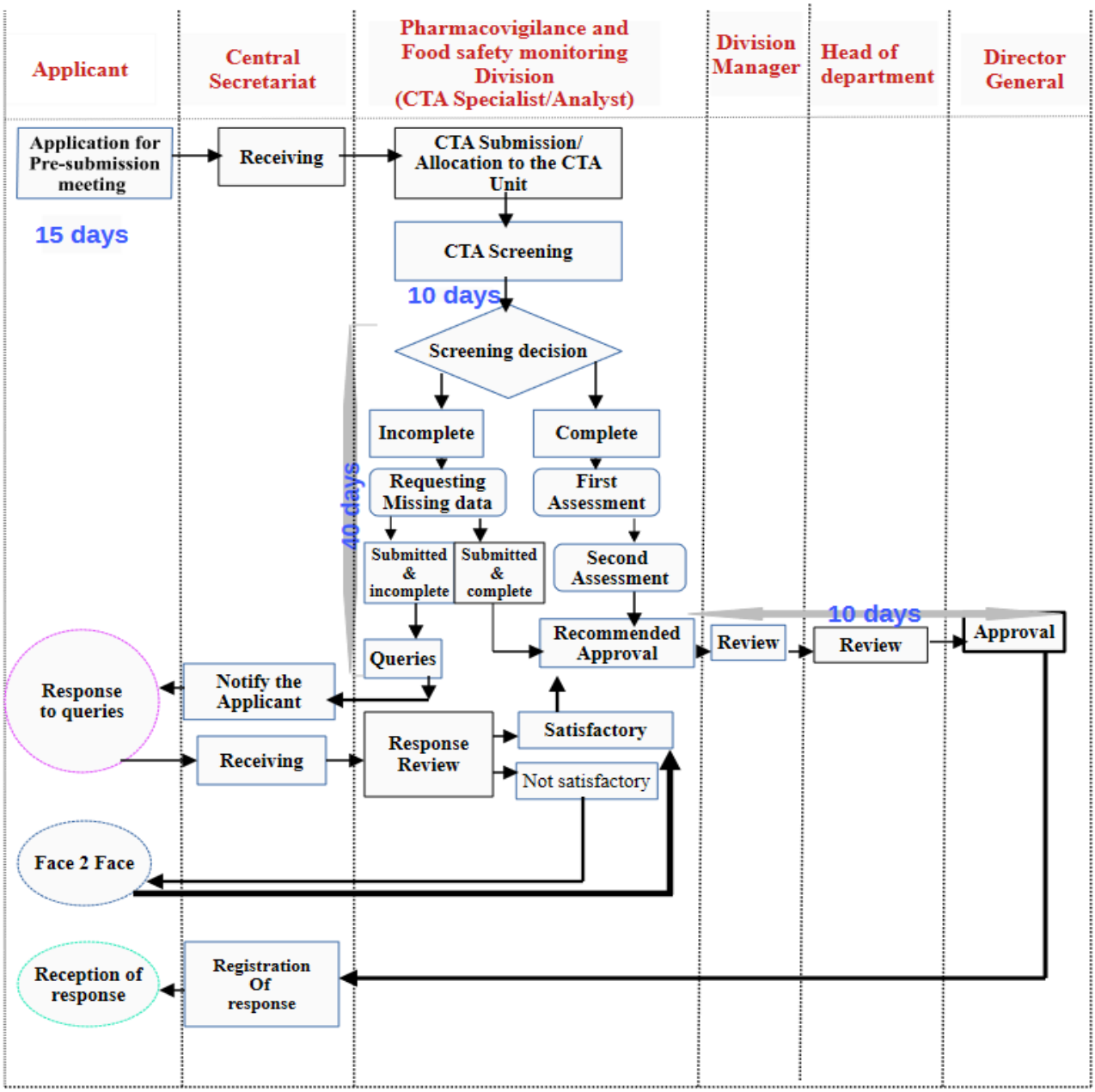
Signature				 Digitally signed by Rwanda FDA (Director General) Date: 2023.04.05 17:16:59 +02'00'
Date	04/04/2023	04/04/2023	05/04/2023	05 / 04 / 2023

ANNEXES

ANNEX-I: CTA REVIEW PROCESS FLOW CHART

Format: QMS/FMT/002 Revision No: 1 Effective Date: 20/06/2022	Department/Division/Office/ Unit	Pharmacovigilance and Food Safety Monitoring Division
Document Type: **Process Flow Chart**		Doc. No : FDISM/PVSM/CHT/002
RWANDA FDA Rwanda Food and Drugs Authority	**Clinical Application Review Process Review**	Revision Number : 01 Revision Date : 03/04/2023 Effective Date : 11/04/2023 Review Due Date : 10/04/2026 Ref Doc. : FDISM/PVSM/GDL/008



ANNEX-II: Screening checklist of clinical trial application

Format: QMS/FMT/002 Revision No: 1 Effective Date: 20/06/2022	Department/Division/Office/ Unit	Pharmacovigilance and Food Safety Monitoring Division
Document Type: **Checklist**		Doc. No : FDISM/PVSM/CKL/008
RWANDA FDA Rwanda Food and Drugs Authority	Title**: Screening of clinical trial application**	Revision Number : 01 Revision Date : 03/04/2023 Effective Date : 11/04/2023 Review Due Date : 10/04/2026 Ref Doc. : FDISM/PVSM/GDL/008

Date of the submission (cover letter)	
Date of receipt (Rwanda FDA stamp)	
Application Reference Number	**NNNN/YYYY (e.g.: 00000/2023)**
Date of Application Screening	
Type CT Application	☐ New Application (CTA) ☐ Amendment Application (CTAA)
Title of Clinical Trial Application	
Protocol Reference Number	
Protocol Version Number (where applicable)	
Name and complete address of CTA Applicant	
Names of Principal Investigator	
Names of Co-Investigator	
Names of Sponsor (If applicable)	
Name and address of the Contract research Organisation (s) (CRO)where the clinical studies proving efficacy and safety of the product were conducted.	
Phase of Trial (if applicable)	
Number of Participants	
Number of Clinical Trial Site(s)	
List of Clinical Trial Sites	
Duration of Clinical Trial	
Name of Investigational Product (IP) Proprietary Product Name (if relevant)	
International Non-proprietary Name (INN) of the Active Ingredient (API), strength, dosage form.	
Name (s) and complete address (es) of the manufacturer (s) of the Investigational	

product (s), including the final product release if different from the manufacturer.	
Investigational Product Therapeutic Indications	
Investigational Product Route of Administration	
Investigational Product Storage Information	
Special Consideration	
Conclusion of the CTA Screening Report	☐ **Recommended for Review** ☐ **Recommended for re-submission**
List of missing regulatory requirements if any	

Module I	**Administrative Information and Protocol Related Information**		
1.1	**Screening of administrative Information**	**Tick as appropriate**	**Comment(s)**
1.1.1	Signed and dated Clinical Trial Application Cover letter	☐ **Yes** ☐ **No**	
1.1.2	Signed and dated clinical trial application form-**ANNEXURE-I**	☐ **Yes** ☐ **No**	
1.1.3	Valid Ethical Clearance Certificate from Rwanda National Ethics Committee	☐ **Yes** ☐ **No**	
1.1.4	Curriculum vitae (CVs) of Principal investigator and Co-investigator(s)	☐ **Yes** ☐ **No**	
1.1.5	Copy of Valid GCP Certificates for both Principal Investigator and co-Principal investigator (s)	☐ **Yes** ☐ **No**	
1.1.6	Signed and dated Joint declaration between Sponsor & Principal Investigator for sufficient funds in the prescribed format (**ANNEXURE-III**)	☐ **Yes** ☐ **No**	
1.1.7	Signed and dated declarations by the Principal investigator and/or Co-investigators (**ANNEXURE-V**)	☐ **Yes** ☐ **No**	
1.1.8	Valid Local Insurance Policy Covering trial participants;	☐ **Yes** ☐ **No**	
1.1.9	Signed and dated Sponsor/ Principal investigator contractual Agreement;	☐ **Yes** ☐ **No**	

1.1.10	Letters of Access authorizing Authority to access related files (Drug Master Files, Site Reference Files) must be submitted;	☐ **Yes** ☐ **No**	
1.1.11	Clinical Trial Site Agreement/contract;	☐ **Yes** ☐ **No**	
1.1.12	Minutes of the discussions and conclusions of the pre-submission meeting or other relevant correspondence with the Authority, if applicable;	☐ **Yes** ☐ **No**	
1.1.13	List of Competent Authorities to which the same application has been submitted and details of decisions, if available	☐ **Yes** ☐ **No** ☐ **NA**	
1.1.14	Evidence of payment of prescribed fees.	☐ **Yes** ☐ **No**	
1.2	**Clinical Trial Protocol-related Information**		
1.2.1	A copy of the final proposed protocol(s), including the version number. The trial protocol must be signed by the sponsor and the investigator prior to the start of the clinical trial (ICH E6 8.2.2).	☐ **Yes** ☐ **No**	
1.2.2	A copy of the Informed Consent Forms (ICFs) in English, French and Kinyarwanda signed and stamped by the Rwanda National Ethics Committee that includes a statement regarding the risks and anticipated benefits to the clinical trial participants as results of their participation in the clinical trial.	☐ **Yes** ☐ **No**	
1.2.3	1. Copy of Participant Information Leaflet (PIL).	☐ **Yes** ☐ **No**	
1.2.4	2. Copy of Case Report Forms (CRFs) to be used (hard copy or electronic)	☐ **Yes** ☐ **No**	
1.2.5	3. Capacity building plan including training and updating of staff involved in the trial.	☐ **Yes** ☐ **No**	
1.2.6	4. Good Clinical Laboratory Practice (GLP) and assay validation.	☐ **Yes**	

		☐ **No**	
1.2.7	5. Signed Charter of DSMB and CVs of Members if applicable	☐ **Yes** ☐ **No** ☐ **NA**	
1.2.8	6. Signed and dated Materials Transfer Agreement (MTA) if applicable;	☐ **Yes** ☐ **No** ☐ **NA**	
Module II	**Screening Information related to the Quality of Investigational Product** (Chemistry, Manufacturing, and Control Summaries)		
2.1	Investigational Product (IP) Dossier containing the Quality Overall Summary and showing the chemistry, manufacture, and control (CMC) as per Common technical document (CTD) format in Annexure-IV, non-clinical data, and Data from previous clinical use (if applicable). In the case of First-in-human (FIH) studies, toxicity and PK/PD reports should be included in the dossier.	☐ **Yes** ☐ **No** ☐ **NA**	
2.2	A copy of the current Investigator's Brochure (IB), supplemented as appropriate with up-to-date safety, non-clinical, and available clinical data.	☐ **Yes** ☐ **No**	
2.3	Copy of valid Good Manufacturing Practice (GMP) Certificate or ISO Certificate OR Copy of the valid manufacturing license for all production steps (not older than 3 years) OR Confirmation document of the authority that the manufacturer complies with PIC/S OR GMP inspection report	☐ **Yes** ☐ **No**	
2.4	A copy of the identification labels for both primary and secondary packaging (outer and inner packaging) of Investigational product labels	☐ **Yes** ☐ **No**	
2.5	Investigational product package Insert/s for mark	☐ **Yes** ☐ **No**	
2.6	Mock-up labels for the Investigational product(s).	☐ **Yes** ☐ **No**	

2.7	Copy of the summary of product characteristics (SmPC) or a copy of the certificate of pharmaceutical product (COPP) of the investigational products	☐ **Yes** ☐ **No**	
2.8	Copy of Certificate of analysis for the batches of the investigational products to be used in a clinical trial if applicable	☐ **Yes** ☐ **No**	
2.9	Composition of the placebo if applicable (placebo-controlled trials**,** information on the placebo is also required including a description of the manufacturing process, a qualitative and quantitative list of ingredients, specifications, batches, stability and facility information	☐ **Yes** ☐ **No** ☐ **NA**	
2.10	Copy of the import authorization in case the investigational product is not imported directly to the trial site	☐ **Yes** ☐ **No** ☐ **NA**	
Module III	**Other Supporting Information**		
3.1	Additional supporting quality information such as publications	☐ **Yes** ☐ **No** ☐ **NA**	
3.2	Literature References	☐ **Yes** ☐ **No** ☐ **NA**	
Overall outcome, comment and conclusion on Clinical Trial application			
NOTE: *The Clinical Trial Application pass the screening stage and accepted for review if the applicable required documents are provided, which will be scored out of 70% accordingly. This should include the signed, dated application letter and forms (2.5%), duly signed protocol with key sections as per prescribed format (40%), updated IB/SmPC(10%), proof of payment of applicable fees (5%), declaration forms(2.5%), agreement between the sponsor and principal investigators(2.5%), Insurance Cover (5%) and RNEC ethical clearance(2.5%).*			
Passed ☐	**Passed with addition requirements** ☐	**Rejected** ☐	
Clinical Trial Screening Report Approvals			
	Names	**Date**	**Signature**

ANNEX-III: Template for review of clinical trial application

Rwanda Food and Drugs Authority
Nyarutarama Plaza, KG 9 Avenue
P.O. Box: 1948 Kigali - Rwanda
Email: info@rwandafda.gov.rw
website: www.rwandafda.gov.rw

QMS Nº: FDISM/PVSM/FMT/003
Revision No: 01
Effective Date: 11/04/2023

Review of Clinical Trial Application

Date of the submission (cover letter)			
Date of receipt (Rwanda FDA stamp)			
Application Reference Number	**NNNN/YYYY (eg. 00000/2023)**		
Reviewers and Review Date			
First Reviewer	Name	Date	Signature
Second Reviewer			
Type CT Application	☐ New Application (CTA) ☐ Amendment Application (CTAA)		
Title of Clinical Trial Application			
Protocol Reference Number			
Protocol Version Number (if applicable)			
Name and complete address of CTA Applicant			
Names of Principal Investigator			
Names of Co-Investigator			
Names of Sponsor and address (If applicable)			
Name and address of the Contract research Organization (s) (CRO) where the clinical studies proving efficacy and safety of the product were conducted.			
Phase of the Trial (if applicable)			
Number of Participants			
Number of Clinical Trial Site(s)			
List of Clinical Trial Sites			
Duration of Clinical Trial			
Name of Investigational Product (IP) Proprietary Product Name (if relevant)			
International Non-proprietary Name (INN) of the Active Ingredient (API), strength, dosage form.			

Name (s) and complete address (es) of the manufacturer (s) of the Investigational product (s), including the final product release if different from the manufacturer.	
Investigational Product Therapeutic Indications	
Investigational Product Route of Administration	
Investigational Product storage Information	
Special Storage consideration	
Overall Conclusion of the CTA Review	☐ **ACCEPTED** ☐ **ADDITIONAL DATA REQUESTED** ☐ **REJECTED**
Points to be communicated with the Clinical Trial Applicant: *Please copy all relevant information to be communicated to the CT applicant in the corresponding letter and save it accordingly*	
Clinical Trial Commitments (if any)	
General remarks to next assessors: *List issues identified during the assessment for the follow up assessment, such as information to be confirmed, to be verified, etc.*	
Recommendations to GCP Inspectors: *List issues identified during the CT assessment phase that require verification during a GCP inspection*	
Recommendations to GCP Inspectors	

SCIENTIFIC REVIEW

1 Background Information

(Insert a brief, concise introduction into the clinical problem and previous treatments and developments, i.e., pertinent data from previous preclinical/clinical pharmacology studies and therapeutic exploratory studies taking into account relevant scientific literature (citations by consecutive numbering, with list at end of this section; important or not readily available references may be included with the paper submission, if appropriate). This section should also contain information on the new drug). Provide rationale for conducting the study in Rwanda

1.1 Low intervention trial

Based on the background information provided, is the trial a low-risk intervention? ☐ **YES** ☐ **NO**

Low-intervention clinical trial means a clinical trial which fulfills all of the following conditions: (a) the investigational medical products, excluding placebos, are authorized; (b) according to the protocol of the clinical trial, (i) the investigational medical products are used in accordance with the terms of the marketing authorisation; or (ii) the use of the investigational medical products is evidence-based and supported by published scientific evidence on the safety and efficacy of those investigational medical products in other countries; and (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the participants compared to normal clinical practice. Source: Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use.

If YES , is the justification provided for the clinical trial intervention as provided by the sponsor is acceptable ? ☐ **YES**
☐ **NO**

If No - tick appropriate box below and **comment**
The investigational medical products used in the study, excluding placebos, are not authorized ☐ **YES**

The investigational medical products are not used in accordance with the terms of the marketing authorization and the use of the investigational medicinal products is not evidence-based ☐ **YES**

The additional diagnostic or monitoring procedures pose more than minimal additional risk or burden to the safety of the participants compared to normal clinical practice ☐ **YES**

Reviewer's comments:

1.1.2 The phase of the trial *(skip if a low intervention):*

1.1. 2.1 The phase of the trial *(skip if a low intervention):*

Reviewer's comments:

1.1.2.2 Therapeutic condition (*Brief description of the disease***):**

Reviewer's comments:

1.1.2.2 Mechanism of action, drug class (*Add a brief description***):**

Reviewer's comments:
1.1.2.3. Status of development: *(Brief discussion of clinical pharmacokinetic data, efficacy and safety data described in the IB from previous trials /previously investigated indications(s) for the IMP(s). Non-clinical studies may also be discussed for early or FIH clinical trials. Consideration should be given to the justification provided based on the non-clinical data, for the proposed starting dose, dose steps, and maximum exposure)*
Reviewer's comments:
1.2 CLINICAL TRIAL RATIONALE: (*Consider what is new in this trial, the clinical relevance, and the medical need that the trial aims to address:*
Reviewer's comments:
2. Review of objective and endpoints of the trial
(Insert the objectives that are the same as the objectives contained in the protocol. Include the primary objective and secondary objectives) ***Primary Objective(s):*** ***Secondary Objective(s):***
Reviewer's comments:
3. Review of Endpoints
(Insert the endpoints that are the same as the endpoints contained in the body of the protocol. Include the primary endpoint and important secondary endpoints) ***Primary Endpoint(s):*** ***Secondary Endpoint(s):***
Reviewer's comments:
4. Review of Design
4.1. *Insert summary description of the type/design of trial to be conducted (e.g. double-blind,*

placebo-controlled, parallel design). Provide a simple summarized snapshot of your study design not to exceed a single page. This section should include a diagram that provides a quick to 1 page. Please present an overview of your study design in a schematic diagram and tables. The data presentation can be adapted depending on the nature of your study and can be customized according to your protocol.

Example: complete the tables with study-specific information and adapt the table(s) to illustrate your study design.

Arm 1	*Sample size*	*Intervention A*
Arm 2	*Sample size*	*Intervention B*

Include instructions for progressing to next phase (if applicable):

Include a schematic diagram to show the design, procedures and stages including study arms, visits, time-points, interventions etc.

4.2. *Summary of the randomization method and procedures to allocate participants to treatment groups;*

4.3. *Blinding (methods of blinding (masking) and other bias reducing techniques to be used);*

4.4. *Summary description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s), including packaging, and labelling of the investigational product(s);*

4.5. *Maintenance of trial treatment randomization codes and procedures for breaking codes;*

4.6. *Total study duration (anticipated starting/ finishing dates);*

4.7. *Expected duration for each subject including post-treatment period etc;*

Reviewer's comments:

5. Study participants

5.1. Healthy volunteers ☐ Patient Participants ☐

5.2. **Age range of trial participants:** Adults (18-65 years) ☐ Children/adolescents ☐ Elderly ≥65 years ☐

5.3. **Gender of trial participants:** Male ☐ Female ☐

5.4. **Use of vulnerable participants** ☐ **YES** ☐ **NO**

If YES, specify which population(s):

Is the inclusion of the vulnerable population is justifiable and the benefit/risk profile is acceptable ☐ **YES** ☐ **NO**

If the trial is for emergency clinical trials, Does the trial provide clinically relevant direct benefit to the participants?

☐ **YES** ☐ **NO** ☐ **NA**

Reviewer's comments:

5.5. *Provide a brief description of specific characteristics of the trial participants (e.g. disease/ stage/ indication/ conditions/ treatment etc.) as applicable and of diagnostic criteria and assessment:*
Reviewer's comments:
5.6. *State the Inclusion criteria:*
5.7. *State the Exclusion criteria:*
Reviewer's comments:
6. Premature Withdrawal / Discontinuation Criteria
6.1. ***Withdrawal criteria:*** **6.1.1.** *Enumeration of all conditions/criteria and management for drug/ patient's withdrawal or (premature) discontinuation, including voluntary withdrawal by subject without prejudice to future treatment by the physician. The type and timing of the data to be collected for withdrawn participants.* **6.1.2.** *State whether and how participants are to be replaced.* **6.1.3.** *The follow-up for participants withdrawn from investigational product treatment/trial Treatment* **6.2.** *State the stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial;*
Reviewer's comments:
7. Review of Quality of the Investigational Products and its Formulation
7.1. *(Brief description of the study drug(s) and formulation to be used in the clinical trial. The relationship to the formulations used in the preclinical and/or other clinical trials should be delineated, as applicable. This may also include disclosure of the formulation intended to be marketed and/or any bridging studies which may be necessary, planned, initiated and/or already performed if different formulations have been used during clinical development.)* **7.2.** *Instructions for safe handling;*
7.3. *State the accountability procedures for the investigational product(s), placebos and comparator(s) and disposal;*
7.4. *State information related to the available safety data and risk benefits assessment*
7.5. *In the case of phase I, II, and III review the investigational product dossier and assess data including the non-clinical data. For marketed product review the SmPC of the investigational products*
Reviewer's comments:

8. Review of Investigational products and Dosage Regimen
8.1. *Rationale for dose selection*
8.2. *Provide the following regarding the treatment(s) to be administered:* **8.3.** *The name(s) of all the product(s):* **8.4.** *Dose(s):* **8.5.** *The dosing schedule(s):* **8.6.** *The route/mode(s) of administration:* **8.7.** *The treatment period(s):* **8.8.** *Follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial:* **8.8.1.** *Concomitant Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial:* **8.8.2.** *Procedures for monitoring participant's compliance:* **8.8.3.** *Wash-out period (Description for pre-, during- and post-trial, as applicable)* **8.8.4.** *The trial includes the investigation of a medical device(s) that is considered acceptable:*
Reviewer's comments:
*The trial includes the investigation of a medical device(s) that is considered acceptable***:**
9. Review of Pre-study Screening and Baseline Evaluation
(Describe in summary the process of clinical validation for participation in the clinical trial, including methodology / schedule of events.
Reviewer's comments:
10. Review of Treatment / Assessment Visits
(Insert the schedule of all events / visits / procedures during the clinical trial)
Reviewer's comments:
11. Review of Efficacy Variables and Analysis
11.1. *Description and validation of primary endpoint(s), i.e. responses/changes from baseline over time in relation to clinical trial events. Description and validation of related secondary changes (secondary endpoints) following from clinical trial events.* **11.2.** *Provide specification of the efficacy parameters.* **11.3.** *Describe the methods and timing for assessing, recording, and analyzing efficacy parameters*
Reviewer's comments:
12. Review of Safety

12.1. *Specification of safety parameters:*

12.2. *The methods and timing for assessing, recording, and analyzing safety parameters:*

12.3. *Procedures for eliciting reports of and for recording and reporting adverse events and intercurrent illnesses.*

12.4. *The type and duration of the follow-up of subjects after adverse events*

12.5. *Summarize the information related to experience of the investigator (s: Curriculum vitae (CVs) of Principal investigator and Co-investigator(s) and GCP certificates to ensure the training, experience and qualification to supervise the implementation of the trial:*

12.6. *RISKS: (Identify potential risks and mitigation strategies (e.g. need for and risks associated with long)*
12.7. *term immunosuppression)*

12.8. *DATA and SAFETY MONITORING PLAN (DSMP):*
(Summarize the Data and Safety Monitoring Plan. Describe measures that will be implemented to minimize risk to study subjects e.g. specific inclusions/exclusions; plans to ensure medical intervention in the case of an adverse event for subjects; plans for surveillance, detection and management of specific adverse events that might or could occur; potential use of an Independent Safety Monitor or Data Safety Monitoring Board (DSMB)
12.9. *Immune Monitoring and immunosuppression: (Describe and justify the plan for immunosuppression and immune monitoring (if applicable)*

Reviewer's comments:

13. Review of Assays/methodologies

13.1. *Briefly describe any specialized assays or methodologies that will be used in this clinical study or supporting study/studies (Provide a more detailed summary of assay methods and summarize assay qualification/validation. Indicate where specialized testing will be conducted):*
13.2. *The names and contact addresses of the laboratories to be used for the study;*
13.3. *State the location of the attached draft Material Transfer Agreements (MTAs) in the submission;*
13.4. *State the duration for long term storage of samples and the area to be stored*

Assessor's comments:

14. Review Statistical analysis plan

14.1. *Specify the planned sample size to be used in the study and its justification*

Planned number of participants to be enrolled:
Are the sample size calculation and justification acceptable? ☐ **YES** ☐ **NO**
Are the trial power and level of significance acceptable? ☐ **YES** ☐ **NO**

Assessor's comments:

14.2. *Summary of description of the statistical methodologies to be used to evaluate the effectiveness of the investigational product, including the hypotheses to be tested, the parameters to be estimated, the assumptions to be made and the level of significance and the statistical model to be used.*

14.3. *Analysis of trial parameters (primary/ secondary endpoints), population, demographics, as applicable.* **14.4.** *Efficacy analysis methods and results of efficacy end-point analysis.* **14.5.** *Safety analysis methods and results of safety end-point analysis.* **14.6.** *Exploratory end-point analysis: evaluation effect(s) (or lack of effects) of relevant biochemical/ pharmacological etc parameters, as applicable.* **14.7.** *Pharmacokinetic endpoint analysis, as applicable.* **14.8.** *Interim analysis and role of Data Safety Monitoring Board, as applicable*
Reviewer's comments:
15. Outcome criteria
(Describe criteria that would define whether you would or would not move forward with the subsequent development plan, based upon primary and designated secondary objectives)
Reviewer's comments:
16. Review of Data management
(Describe procedures for recording, processing, handling, and retaining raw data and other study documentation)
Reviewer's comments:
17. Review of Monitoring plan
(Summary of the monitoring plan) *State the location of the detailed monitoring plan in the submission*
Reviewer's comments:
18. Ethical considerations
18.1. *State the ethical clearance reference number and institutions that have approved the trial Rwanda National Research Ethics Committee ethical clearance: RNEC ethical clearance number and Date:*
18.2. ***Insurance Details :*** **18.2.1.** *Insert local Insurance Company name and address:* **18.2.2.** *policy cover number:* **18.2.3.** *Validity:* **18.2.4.** *Expiry Date:* **18.2.5.** *State the location of the Insurance cover in the submission:* **18.2.6.** *List of Covered risks:*
18.3. ***Participant Information sheets and Informed Consent forms:*** *The contents should be as per ICH GCP guidelines, these guidelines and declaration of Helsinki)* **18.3.1.** *.State the version number and dates for both English and Kinyarwanda versions* **18.3.2.** *State the location of the Participant Information sheets and Informed Consent forms in the submission*
18.4. *State the amount to be reimbursed to the participants:*
18.5. *Treatment and/or management of participants and their disease condition(s) after completion of trial*
18.6. *Follow-up of trial study participants after the conclusion of the trial*

18.7. *In case of transfer of materials, provide Material Transfer Agreement (MTA) highlighting among other things, the following:*
18.8. *Identification of the provider and recipient*
18.9. *Identification of the material and the volume of material*
18.10. *Definition of the trial and how the material will and will not be used.*
18.11. *Maintenance of confidentiality of background or supporting data or information, if any*
18.12. *Indemnification and warranties (where applicable)*
18.13. *Details on post-trial access to the products*
Assessor's comments:
19. Benefit/risk assessment
The protocol contains an acceptable evaluation of the anticipated benefits and risks of participating in the trial ☐ **YES** ☐ **NO** Are the measures proposed to address the known and potential risks of participating in the trial and to protect participants acceptable? ☐ **YES** ☐ **NO**
Reviewer's comments: *Based on medical and ethical principles the anticipated benefits to the participants or to public health do not justify the foreseeable risks and inconveniences, or compliance with this condition is not constantly monitored Rights of the participants to physical and mental integrity, and privacy are insufficiently safeguarded in the study The clinical trial has not been designed to involve as little pain, discomfort, fear and any other foreseeable risk as possible, or both the risk threshold and the degree of distress are not defined in the protocol or are not monitored*
GENERAL COMMENTS ON THE REVIEW

ANNEX-IV: Template of clinical trial approval certificate

RWANDA FDA
Rwanda Food and Drugs Authority

Nyarutarama Plaza, KG 9 Avenue
P.O. Box: 1948 Kigali - Rwanda
Email: info@rwandafda.gov.rw
website: www.rwandafda.gov.rw

QMS N°: FDISM/PVSM/FMT/001
Revision No: 1
Effective Date: 11/04/2023

CLINICAL TRIAL APPROVAL CERTIFICATE

(Made under law No. 003/2018 of 09/02/2018 establishing the Rwanda FDA and determining its mission, organization, and functioning in its article 8, paragraph 7 and article 9, paragraph 2)

Clinical Trial Approval Certificate N°: [000/CTA/0000-YYYY/FDA/0000-YYYY]

This is to certify that the clinical trial described below has been approved in Rwanda subject to the conditions indicated in this certificate.

Protocol Title: ……

Protocol Number and version: ……..

Name of the Investigational product (s):

Investigational Product(s)/Intervention (s)	**Comparator (s)**
…… ……....	…… ……

Clinical Trial site (s): …….....
…….....
…….....

Name of the Principal Investigator(s): …….....

CRO/Research Institution (s): …….....

Sponsor's name: …….....

Validity from: [DD/MM/YYYY] to [DD/MM/YYYY]

Issued at Kigali, on [DD/MM/YYYY]

<insert signature and stamp>

<Insert the names of approving Authority >
Director General

Key Conditions for compliance

1. To notify Rwanda FDA about trial initiation within three (3) months;
2. To provide sufficient information to participants before recruitment;
3. To obtain informed consent from the participant prior to enrolment;
4. To comply with eligibility criteria while recruiting participants as per the approved trial protocol;
5. To seek approval of all substantial amendments related to the trial or trial protocol prior to the implementation;
6. To notify Rwanda FDA of any Serious Adverse Events (SAEs) as soon as possible but not later than seven (7) calendar days using ADR/AEFI reporting form and submit a complete report within eight (8) next calendar days;
7. To submit the progress and final report of the clinical trial to Rwanda FDA at the prescribed timelines;
8. To apply for renewal of Clinical Trial Approval Certificate one month before its expiration.

ANNEX-V: Template of clinical trial approval certificate for renewal

RWANDA FDA
Rwanda Food and Drugs Authority

Nyarutarama Plaza, KG 9 Avenue
P.O. Box: 1948 Kigali - Rwanda
Email: info@rwandafda.gov.rw
website: www.rwandafda.gov.rw

QMS N°: FDISM/PVSM/FMT/036
Revision No: 0
Effective Date: 11/04/2023

CLINICAL TRIAL APPROVAL CERTIFICATE

(*Made under law No. 003/2018 of 09/02/2018 establishing the Rwanda FDA and determining its mission, organization, and functioning in its article 8, paragraph 7 and article 9, paragraph 2)*

This is to certify that the Clinical trial Approval Certificate No**: [000/CTA/0000-YYYY/FDA/0000-YYYY]** of **[DD/MM/YYYY]** of the clinical trial described below has been renewed subject to the conditions indicated in this certificate.

Protocol Title: ……

Protocol Number and version: ……..

Name of the Investigational product (s):

Investigational Product(s)/Intervention (s)	**Comparator (s)**
…… …….....	…… ……

Clinical Trial site (s): ……..
……..
……..

Name of the Principal Investigator(s): ……..

CRO/Research Institution (s): ……..
Sponsor's name: ……..

Validity from: [DD/MM/YYYY] to [DD/MM/YYYY]

Issued at Kigali, on [DD/MM/YYYY]

<insert signature and stamp>

<Insert the names of approving Authority >
Director General

Key Conditions for compliance

1. To notify Rwanda FDA about trial initiation within three (3) months;
2. To provide sufficient information to participants before recruitment;
3. To obtain informed consent from the participant prior to enrolment;
4. To comply with eligibility criteria while recruiting participants as per the approved trial protocol;
5. To seek approval of all substantial amendments related to the trial or trial protocol prior to the implementation;
6. To notify Rwanda FDA of any Serious Adverse Events (SAEs) as soon as possible but not later than seven (7) calendar days using ADR/AEFI reporting form and submit a complete report within eight (8) next calendar days;
7. To submit the progress and final report of the clinical trial to Rwanda FDA at the prescribed timelines;
8. To apply for renewal of Clinical Trial Approval Certificate one month before its expiration.

ANNEX-VI: Template of additional data or query response

Rwanda Food and Drugs Authority

Nyarutarama Plaza, KG 9 Avenue
P.O. Box: 1948 Kigali - Rwanda
Email: info@rwandafda.gov.rw
website: www.rwandafda.gov.rw

QMS Nº: FDISM/PVSM/FMT/004
Revision No: 01
Effective Date: 11/04/2023

Template of additional data or query response

Date of the submission (cover letter)			
Date of receipt (Rwanda FDA stamp)			
Application Reference Number	**NNNN/YYYY (eg. 00000/2023)**		
Reviewers and Review Date			
First Reviewer	Name	Date	Signature
Second Reviewer			
Type CT Application	☐ New Application (CTA) ☐ Amendment Application (CTAA)		
Title of Clinical Trial Application			
Protocol Reference Number			
Protocol Version Number (if applicable)			
Name and complete address of CTA Applicant			
Names of Principal Investigator			
Names of Co-Investigator			
Names of Sponsor and address (If applicable)			
Name and address of the Contract research Organization (s) (CRO) where the clinical studies proving efficacy and safety of the product were conducted.			
Phase of the Trial (if applicable)			
Number of Participants			
Number of Clinical Trial Site(s)			
Duration of Clinical Trial			

Name of Investigational Product (IP) Proprietary Product Name (if relevant)	
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.	
Name (s) and complete address (es) of the manufacturer (s) of the Investigational product (s), including the final product release if different from the manufacturer.	
Name (s) and complete address (es) of the manufacturer (s) of the Investigational product (s), including the final product release if different from the manufacturer.	
Investigational Product Therapeutic Indications	
Investigational Product Route of Administration	
Investigational Product storage Information	
Special Storage consideration	
Overall Conclusion of the CTA Review	☐ **ACCEPTED** ☐ **ADDITIONAL DATA REQUESTED** ☐ **REJECTED**
Points to be communicated with the Clinical Trial Applicant: *Please copy all relevant information to be communicated to the CT applicant in the corresponding letter and save it accordingly*	
Clinical Trial Commitments (if any)	
General remarks to next assessors: *List issues identified during the assessment for the follow up assessment, such as information to be confirmed, to be verified, etc.*	
Recommendations to GCP Inspectors: *List issues identified during the CT assessment phase that require verification during a GCP inspection*	
Recommendations to GCP Inspectors: *List issues identified during the CT assessment phase that require verification during a GCP inspection*	
Question from Previous CT Assessor (1)	

Response from CT Applicant (1)
Comment from CT Assessor (1)
Question from Previous CT Assessor (2)
Response from CT Applicant (2)
Comment from CT Assessor (2)
Question from Previous CT Assessor (3)
Response from CT Applicant (3)
Comment from CT Assessor (3)
Question from Previous CT Assessor (4)
Response from CT Applicant (4)
Comment from CT Assessor (4)
Question from Previous CT Assessor (5)
Response from CT Applicant (5)

Comment from CT Assessor (5)

ANNEX-VII: Template for Investigational Product Quality Review

Rwanda Food and Drugs Authority

Nyarutarama Plaza, KG 9 Avenue
P.O. Box: 1948 Kigali - Rwanda
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QMS Nº: FDISM/PVSM/FMT/005
Revision No: 01
Effective Date: 11/04/2023

Investigational Product Quality Review

Date of the submission (cover letter)			
Date of receipt (Rwanda FDA stamp)			
Application Reference Number	**NNNN/YYYY (eg. 00000/2023)**		
Reviewers and Review Date			
First Reviewer	Name	Date	Signature
Second Reviewer			
Type CT Application	☐ New Application (CTA) ☐ Amendment Application (CTAA)		
Title of Clinical Trial Application			
Protocol Reference Number			
Protocol Version Number (if applicable)			
Name and complete address of CTA Applicant			
Names of Principal Investigator			
Names of Co-Investigator			
Names of Sponsor and address (If applicable)			
Name and address of the Contract research Organization (s) (CRO) where the clinical studies proving efficacy and safety of the product were conducted.			
Phase of the Trial (if applicable)			
Number of Participants			
Number of Clinical Trial Site(s)			
Duration of Clinical Trial			
Name of Investigational Product (IP) Proprietary Product Name (if relevant)			

International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.	
Name (s) and complete address (es) of the manufacturer (s) of the Investigational product (s), including the final product release if different from the manufacturer.	
Name (s) and complete address (es) of the manufacturer (s) of the Investigational product (s), including the final product release if different from the manufacturer.	
Investigational Product Therapeutic Indications	
Investigational Product Route of Administration	
Investigational Product storage Information	
Special Storage consideration	
Overall Conclusion of the CTA Review	☐ **ACCEPTED** ☐ **ADDITIONAL DATA REQUESTED** ☐ **REJECTED**
Points to be communicated with the Clinical Trial Applicant: *Please copy all relevant information to be communicated to the CT applicant in the corresponding letter and save it accordingly*	
Clinical Trial Commitments (if any)	

REVIEW OF QUALITY OF INVESTIGATIONAL PRODUCT			
1	**GMP Compliance**		
	Valid Manufacturing License issued by the competent Authority in the country of origin		☐ YES ☐ NO
	Valid Good Manufacturing License Issued by the competent Authority in the country of origin		☐ YES ☐ NO
	Registered, non-modified product only SmPC has been provided		☐ YES ☐ NO
	Does the Drug substance have a monograph?		☐ YES ☐ NO
	Does the active substance belong to an authorised drug product in the EU/USA/Ph.Int/Japan?		☐ YES ☐ NO
	None of the above (full S Section is needed		
2.3 S	**Drug substance**		
2.3.S.1	***General information***		
	S.1.1 Nomenclature		
	Paste the chemical name, other names or codes		☐ YES ☐ NO ☐ NA
	Comments:		
	S.1.2 Structure		
	*Does the submitted documentation cover this subsection adequately**?***		☐ YES ☐ NO ☐ NA

	✓ *For chemicals: paste the chemical structure /stereochemistry.* ✓ *For biologicals: provide a brief description of the predicted structure*	
	Comments:	
	S.1.3 General properties	
	Does the information submitted cover this subsection adequately? ✓ *For chemicals, list the physicochemical properties likely to affect pharmacological or toxicological safety, eg solubility, pKa, etc* ✓ *For biologicals, summarize the proposed mechanism of action*	☐ YES ☐ NO ☐ NA
	Comments:	
2.3. S.2	***Manufacture***	
	S.2.1 Manufacturer(s)	
	Are the production sites clearly identified on GMP Certificate?	☐ YES ☐ NO ☐ NA
	Comments:	
	S.2.2 Description of the manufacturing process and process controls	
	Substance: are the manufacturing processes and their controls adequately described? ✓ *For chemical IMPs, brief summary of the process including critical steps and process controls, stereochemistry of the starting materials, solvents, metal catalysts, and critical reagents. Paste the flow chart of the manufacturing process* ✓ *For biological IMPs, provide the flow chart of the manufacturing process including in-process testing, batch size/scale, reprocessing. Each step should be justified*	☐ YES ☐ NO ☐ NA
	Comments:	
	S.2.3. Control of materials	
	Is the control of materials adequately described? ✓ *Include information on critical materials and their control* ✓ *For biological IMPs, include summary of source [materials], history of generation of cell substrate, the cell bank system, characterization and testing, and cell substrate stability and/or summary of source, history and generation of virus seed material* ✓ *If applicable, summary of compendial and non-compendial raw materials or materials of human origin*	☐ YES ☐ NO ☐ NA
	Comments:	

	S.2.4 Control of critical steps and intermediates	
	Is the control of critical steps and intermediates adequately described?	☐ YES ☐ NO ☐ NA
	Comments:	
	S.2.5 Process validation and/or evaluation	
	Is the process validation adequately described?	☐ YES ☐ NO ☐ NA
	Comments:	
	S.2.6. Manufacturing process development	
	Is the manufacturing process development adequately described? ✓ *Significant differences from the manufacturing process of toxicological or previous clinical batches should be summarized (if applicable)* ✓ *For biological IMPs: comment on comparability data (if relevant)*	☐ YES ☐ NO ☐ NA
	Comments:	
2.3 S.3	**Characterization**	
	S.3.1 Elucidation of the structure and other characteristics	
	Is the drug substance sufficiently characterised? *Summarize the methods used to characterize the product*	☐ YES ☐ NO ☐ NA
	Comments	
	S.3.2 Impurities	
	Are impurities sufficiently characterised? ✓ *For chemical IMPs: state if it complies with a Pharmacopeia and if so, with which one (US, EU, JP, other) or summarize the impurities from the degradation products, potential genotoxic impurities of solvents and catalysts (if applicable), residual solvents used for the purification of small molecules, and any control issues* ✓ *Summarize process and product-related impurities and any issues with control*	☐ YES ☐ NO ☐ NA
	Comments:	
2.3. S.4	***Control of the drug substance***	
	S.4.1 Specification(s)	
	The specifications proposed for the drug substance, including appropriate limits, are satisfactory? *For those IMPs that are not controlled by a pharmacopeial monograph, copy and paste the proposed specifications, tests*	☐ YES ☐ NO ☐ NA

	methods and limits from the IMPD	
	Comments:	
	S.4.2 Analytical procedures	
	Are the analytical methods adequately described?	☐ YES ☐ NO ☐ NA
	Comments:	
	S.4.3 Validation of analytical procedures	
	Phase I trials *The suitability of the methods is commensurate with the stage of development. The acceptance limits and parameters to validate the analytical methods are presented:*	☐ YES ☐ NO ☐ NA
	For phase II/III trials *The suitability of methods is commensurate with the stage of development and clearly explained. A summary of the validation results is provided:*	☐ YES ☐ NO ☐ NA
	Comments:	
	S.4.4 Batch analyses	
	Data for representative batch analyses are provided for all the relevant manufacturing process, and for each drug substance manufacturer: *Comment on the acceptability of the batch data provided in support of the clinical trial material*	☐ YES ☐ NO ☐ NA
	Comments:	
	S.4.5 Justification of the specification (s)	
	The justification for the specifications is acceptable? *Summarize the critical specifications and acceptance criteria*	☐ YES ☐ NO ☐ NA
	Comments:	
2.3. S.5	**Reference standards or materials**	
	<u>Reference standard</u> *A suitable reference standard is adequately described:*	☐ YES ☐ NO ☐ NA
	Comments:	
2.3. S.6	**Container closure system**	
	The container closure system for the drug substance is properly characterised and suitable:	☐ YES ☐ NO ☐ NA
	Comments:	
2.3. S.7	**Stability**	

	The stability for the drug substance is satisfactory and properly described for all the relevant manufacturing processes: ✓ *Indicative text: amend or delete as necessary* ✓ *List of proposed shelf-life/retest period and storage conditions of the drug substance.* ✓ *Summary of stability studies provided in support of the proposed shelf-life.* ✓ *State number of months for which data is available.* ✓ *Comment on whether trends or out of spec results are observed.*	☐ YES ☐ NO ☐ NA
	The extension of shelf-life will be made without substantial amendment	☐ YES ☐ NO ☐ NA
	If yes, the extension will be made in accordance with a registered protocol	☐ YES ☐ NO ☐ NA
	Comments:	
3.2. P	**Drug product (repeat this section for additional IMPs)**	
3.3. P.1	***Description and composition of the investigational medical product***	
	The description and composition are adequate: *Provide the qualitative and quantitative composition of the IMP*	☐ YES ☐ NO ☐ NA
3.3. P.2	***Pharmaceutical development***	
	The pharmaceutical development is adequately described:	☐ YES ☐ NO ☐ NA
	Comments:	
3.3. P.3	***Manufacture***	
	P.3.1 Manufacturer(s)	
	The manufacturing sites are clearly identified:	☐ YES ☐ NO ☐ NA
	Comments:	
	P.3.2 Batch formula	
	The batch formula is appropriately described: *Comment on the batch size proposed*	☐ YES ☐ NO ☐ NA
	Comments:	
	P.3.3 Description of the manufacturing process and process controls	
	The manufacturing process and process control are adequately described: ✓ *Add a brief summary of the manufacturing process including critical steps* ✓ *and in-process controls or paste the flow chart of the manufacturing process*	☐ YES ☐ NO ☐ NA
	Comments:	

	P.3.4 Controls of critical steps and intermediates	
	The controls of critical steps and intermediates are adequately described:	☐ YES ☐ NO ☐ NA
	Comments:	
	P.3.5 Process validation and/or evaluation	
	The validation processes are adequately described: *If relevant, confirm if the process validation for non-standard sterilization* *and manufacturing processes are provided*	☐ YES ☐ NO ☐ NA
3.2. P.4	**Control of excipients**	
	P.4.1 Specifications	
	For excipients not described in current pharmacopoeias *The specifications and acceptance criteria provided are appropriate:*	☐ YES ☐ NO ☐ NA
	Comments:	
	P.4.2 Analytical procedures	
	The analytical procedures are adequately described:	☐ YES ☐ NO ☐ NA
	Comments:	
	P.4.3 Validation of the analytical procedures	
	The analytical procedures are adequately validated:	☐ YES ☐ NO ☐ NA
	Comments:	
	P.4.4 Justification of the specifications	
	The justification provided for the specifications of excipients and their limits is satisfactory: *Comment on the acceptability of the batch data provided in support of the* *clinical trial material*	☐ YES ☐ NO ☐ NA
	Comments:	
	P.4.5 Excipients of animal or human origin	
	The IMP contains excipients of animal origin:	☐ YES ☐ NO ☐ NA
	Safety information on transmissible spongiform encephalopathies (TSE) is provided and deemed satisfactory:	☐ YES ☐ NO ☐ NA
	Comments:	
	P.4.6 Novel excipients	

	Excipients are appropriately controlled: *Confirm compliance for excipients described in the pharmacopeia. For those not described therein, check if adequate information on quality control was provided*	☐ YES ☐ NO ☐ NA
3.2. P.5	**P.5 Control of the drug product**	
	P.5.1 Specifications	
	Satisfactory specifications for the drug product, including appropriate limits, are proposed: *Copy and paste the proposed drug product specifications, including limits,* *from the IMPD*	☐ YES ☐ NO ☐ NA
	P.5.2 Analytical procedures	
	***Are the analytical methods adequately described*?**	☐ YES ☐ NO ☐ NA
	Comments:	
	P.5.3 Validation of analytical procedures	
	Phase I trials *The suitability of the methods is commensurate with the stage of development. The acceptance limits and parameters to validate the analytical methods are presented:*	☐ YES ☐ NO ☐ NA
	For phase II/III trials *The suitability of methods is commensurate with the stage of development and clearly explained. A summary of the validation results is provided*:	☐ YES ☐ NO ☐ NA
	Comments:	
	P.5.4 Batch analyses	
	Data for representative batch analyses are provided for all the relevant manufacturing process, and for each drug product manufacturer:	☐ YES ☐ NO ☐ NA
	Comments:	
	P.5.5 Characterizations of impurities	
	The information provided for impurities is acceptable: *Discuss additional impurities/degradants that are not part of the drug substance and whether they are properly controlled by the drug product specification*	☐ YES ☐ NO ☐ NA
	Comments:	
	P.5.6 Justification of specification(s)	
	The justification for the drug product specifications and limits is acceptable	☐ YES ☐ NO ☐ NA
	Comments:	
3.2. P.6	**Reference standards or materials**	

	Reference standard *A suitable reference standard is adequately described:*	☐ YES ☐ NO ☐ NA
	Comments:	
3.2. P.7	**P.7 Container closure system**	
	The container closure system for the drug product is properly characterised and suitable:	☐ YES ☐ NO ☐ NA
	Comments:	
3.2. P.8	**Stability**	
	P.8.1 Stability summary and conclusions	
	P.8.2 post-approval stability protocol and stability commitment	
	P.8.3 Stability data	
	The drug product has undergone appropriate stability tests: ✓ *Indicative text: amend or delete as necessary* ✓ *Proposed shelf-life and storage conditions of the IMP?* ✓ *Summary of stability studies provided in support of the proposed shelf-life* ✓ *(delete/amend columns as appropriate). State the number of months for which data are available.* ✓ *Comment whether trends or out of specifications results were observed.*	☐ YES ☐ NO ☐ NA
	The extension of shelf-life will be made without substantial amendment:	☐ YES ☐ NO ☐ NA
	If yes, extension to be made in accordance with a registered protocol:	☐ YES ☐ NO ☐ NA
	Comments:	
	Comparator (comparator 1, comparator 2 etc – replicate individual sections of the review form, 2.S and 2.P as required)	
	The data provided for the comparator are acceptable: *For modified authorized comparators: add a description and justification of the modification*	☐ YES ☐ NO ☐ NA
	Comments:	
	Placebo (PL1, PL2 etc, - replicate this section as required)	
	The information provided on the placebo is acceptable: Or (delete if not applicable): *No information was provided, but this is acceptable because the product has the same composition as the IMP. It's manufactured by the same manufacturer and is not sterile* *Summary of information provided and its acceptability:* *P.1 Description and composition* *P.2 Pharmaceutical development* *P.3 Manufacture* *P.4 Control of excipients* *P.5 Control of placebo product*	☐ YES ☐ NO ☐ NA

	P.6 Container closure system *P.7 Stability*	
	Comments:	
	Auxiliary medical products– replicate the individual sections of the review form, 3.S and 3.P as required	
	The quality data provided for non-authorised auxiliary medical products are acceptable	☐ YES ☐ NO ☐ NA
	Labelling	
	Is the proposed labelling in line with national requirements?	☐ YES ☐ NO ☐ NA
	Comments:	
	Blinding	
	Refer to the statistical methodology given in the clinical trial protocol	
	Reviewer's overall conclusions on the quality part	
	The quality data are acceptable:	☐ YES ☐ NO ☐ NA
	Supplementary information has to be provided	☐ YES ☐ NO ☐ NA
	Refer to the requests for additional information	☐ YES ☐ NO ☐ NA

ANNEX-VIII: Template for review of non-clinical data

Rwanda Food and Drugs Authority

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QMS Nº: FDISM/PVSM/FMT/006
Revision No: 01
Effective Date: 11/04/2023

Review of non-clinical data

Date of the submission (cover letter)			
Date of receipt (Rwanda FDA stamp)			
Application Reference Number	**NNNN/YYYY (eg. 00000/2023)**		
Reviewers and Review Date			
First Reviewer	Name	Date	Signature
Second Reviewer			
Type CT Application	☐ New Application (CTA) ☐ Amendment Application (CTAA)		
Title of Clinical Trial Application			
Protocol Reference Number			
Protocol Version Number (if applicable)			
Name and complete address of CTA Applicant			
Names of Principal Investigator			
Names of Co-Investigator			
Names of Sponsor and address (If applicable)			
Name and address of the Contract research Organization (s) (CRO) where the clinical studies proving efficacy and safety of the product were conducted.			
Phase of the Trial (if applicable)			
Number of Participants			
Number of Clinical Trial Site(s)			
Duration of Clinical Trial			
Name of Investigational Product (IP) Proprietary Product Name (if relevant)			
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.			
Name (s) and complete address (es) of the manufacturer (s) of the Investigational			

product (s), including the final product release if different from the manufacturer.	
Name (s) and complete address (es) of the manufacturer (s) of the Investigational product (s), including the final product release if different from the manufacturer.	
Investigational Product Therapeutic Indications	
Investigational Product Route of Administration	
Investigational Product storage Information	
Special Storage consideration	
Overall Conclusion of the CTA Review	☐ **ACCEPTED** ☐ **ADDITIONAL DATA REQUESTED** ☐ **REJECTED**
Points to be communicated with the Clinical Trial Applicant: *Please copy all relevant information to be communicated to the CT applicant in the corresponding letter and save it accordingly*	
Clinical Trial Commitments (if any)	

REVIEW OF NON-CLINICAL DATA or PRECLINICAL DATA (Phase I & II)		
1.0	**Introduction**	
	Provide a brief overview of the preclinical package and any relevant preclinical issues identified in previous assessments *IMPs with an MA: indicate if the IMP is going to be used according to the marketing authorization, of if the population/dose/dosing regimen/indication/duration is different. If the latter, describe the supporting information in the relevant sections*	
2.0	**Pharmacology**	
	2.1 Primary pharmacodynamics	
	The pharmacology studies provide the pharmacological basis for the proposed trial	☐ YES ☐ NO ☐ NA
	Were relevant in vitro and/or in vivo models studied?	☐ YES ☐ NO ☐ NA
	Is the intended pharmacological effect expected/ possible at clinical exposure?	☐ YES ☐ NO ☐ NA
	Were pharmacologically active major metabolites identified?	☐ YES ☐ NO ☐ NA
	Is the IMP a first-in-class compound?	☐ YES ☐ NO ☐ NA
	Provide a brief outline of the in vivo/invitro studies performed to evaluate primary pharmacodynamics and the results:	
	2.2 Secondary pharmacodynamics	
	The studies described in this section identified off-target effects	☐ YES ☐ NO ☐ NA
	Are off-target effects expected / possible at clinical exposure?	☐ YES ☐ NO ☐ NA
	Comments:	

	2.3 Safety pharmacology			
	System	*Study type*	*Issues identified*	*Major findings*
	Cardiovascular		☐ YES ☐ NO ☐ NA	
	Respiratory		☐ YES ☐ NO ☐ NA	
	CNS		☐ YES ☐ NO ☐ NA	
	Other		☐ YES ☐ NO ☐ NA	
	Did the safety pharmacology studies identify significant concerns?			☐ YES ☐ NO ☐ NA
	Do sufficient margins of exposure exist for planned clinical exposure?			☐ YES ☐ NO ☐ NA
	Comments:			
	2.4 Pharmacodynamic drug interactions			
	Have potential pharmacodynamics drug interactions identified			☐ YES ☐ NO ☐ NA
	Describe briefly any in vitro/in vivo studies performed and their results if any			
	Comments:			
3.0	**Pharmacokinetics**			
	3.1 Methods of analysis			
	Are the methods of analysis and their sensitivities adequate?			☐ YES ☐ NO ☐ NA
	Comments:			
	3.2 Absorption, distribution, metabolism & excretion			☐ YES ☐ NO ☐ NA
	System	***Issues identified***	***Findings***	
	Absorption	☐ YES ☐ NO ☐ NA		
	Distribution	☐ YES ☐ NO ☐ NA		
	Metabolism	☐ YES ☐ NO ☐ NA		
	Excretion	☐ YES ☐ NO ☐ NA		
	Do the ADME studies identify significant concerns?			☐ YES ☐ NO ☐ NA
	Major human metabolites were identified			☐ YES ☐ NO ☐ NA
	Unique human metabolites were identified			☐ YES ☐ NO ☐ NA
	Add a brief description of the studies performed and the results. A cross-reference to sections 4.4.3, 4.4.5, and 4.4.6 (toxicokinetic) is enough			
	Comments:			
	3.3 Pharmacokinetic drug interactions (enzymes, transporter, other)			
	Target evaluated	*Interaction identified*	*Findings*	
	Enzyme inhibition	☐ YES ☐ NO ☐ NA		

	Enzyme induction	☐ YES ☐ NO ☐ NA	
	Transporter	☐ YES ☐ NO ☐ NA	
	Co-pathways	☐ YES ☐ NO ☐ NA	
	Potential for PK drug interactions is indicated at therapeutic dose		☐ YES ☐ NO ☐ NA
	The potential interactions have been highlighted to investigators and relevant information is included in the IB/study protocol		☐ YES ☐ NO ☐ NA
	Describe briefly the invitro/invivo studies performed and discuss the results:		
	3.*4 Other pharmacokinetic studies (e.g. PK of metabolite, novel excipients, genomic integration and inadvertent germline transmission of gene transfer vectors)*		
	Were other PK studies performed?		☐ YES ☐ NO ☐ NA
	Do these studies identify concerns?		☐ YES ☐ NO ☐ NA
	Describe briefly any additional invitro/invivo studies performed and the results:		
4.0	**Toxicology**		
	4.1 Animal species selection/study design		
	Toxicologically relevant animal species studied		☐ YES ☐ NO ☐ NA
	The studied species show similar pharmacology to human		☐ YES ☐ NO ☐ NA
	The studied species show similar PK to humans		☐ YES ☐ NO ☐ NA
	The studies were sufficiently well-designed		☐ YES ☐ NO ☐ NA
	Describe briefly the preclinical toxicity studies performed, the relevant guidelines (ICH M3 (R2), S6 (R1), S9) used, and any deviations for any guidelines. Any study-specific guidelines should be discussed in this section:		

	4.2. Single dose toxicity			
	Species	**Dose/Route**	**NO(A)EL/LOEL /MNTD (delete as appropriate)**	**Major findings**

	Were significant toxicities identified?	☐ YES ☐ NO ☐ NA
	Do sufficient margins of exposure exist for planned clinical exposure	☐ YES ☐ NO ☐ NA
	Brief description of any studies performed. The results should be presented in the tablets:	

	4.3 Repeat-dose toxicity			
	Species	**Dose/Route**	**NO(A)EL/LOEL /MNTD (delete as appropriate)**	**Major findings**
	Do sufficient margins of exposure exist for planned clinical exposure			☐ YES ☐ NO ☐ NA
	Does the duration of treatment support the proposed trial duration			☐ YES ☐ NO ☐ NA
	Brief description of any studies performed. The results should be presented in the tables:			
	4.4 Genotoxicity			
	Type of test/study	*Test system*	*Results*	
	Gene mutations in bacteria		☐ Positive ☐ Negative ☐ Equivocal	
	In Vitro Mammalian assay		☐ Positive ☐ Negative ☐ Equivocal	
	In vivo genotoxicity test		☐ Positive ☐ Negative ☐ Equivocal	
	Additional assays		☐ Positive ☐ Negative ☐ Equivocal	
	Do the submitted data indicate genotoxic potential?			☐ YES ☐ NO ☐ NA
	Comments:			
	4.5 Carcinogenicity			
	Do studies identify potential for carcinogenicity?			☐ YES ☐ NO ☐ NA
	Do sufficient margins of exposure exist for planned clinical exposure?			☐ YES ☐ NO ☐ NA
	4.6 Reproductive and developmental toxicity Summary			
	System	***Toxicities identified***	***Findings***	
	Fertility and early embryonic development	☐ YES ☐ NO ☐ NA		
	Embryo-fetal development	☐ YES ☐ NO ☐ NA		
	Prenatal and postnatal	☐ YES ☐ NO ☐ NA		

	development, including maternal function		
	Do sufficient margins of exposure exist for planned clinical exposure?		☐ YES ☐ NO ☐ NA
	Comments:		
	4.6.1 Juvenile toxicity studies		
	The studies utilised animals in the appropriate age range		☐ YES ☐ NO ☐ NA
	The studies identified additional/enhanced juvenile toxicities		☐ YES ☐ NO ☐ NA
	Do sufficient margins of exposure exist for planned clinical exposure?		☐ YES ☐ NO ☐ NA
	Comments:		
	4.6.2 Other studies		
	The studies identified potential toxicities		☐ YES ☐ NO ☐ NA
	Do sufficient margins of exposure exist for planned clinical exposure?		☐ YES ☐ NO ☐ NA
	Comments:		
	4.6.3 Recommendations for contraception measures		
	Investigational medicinal products	*Non-clinical data summary*	☐
		Suspected/ demonstrated teratogenic or fetotoxic effects	☐
		Genotoxic	☐
		Insufficient data	☐
		Demonstrated embryo-fetotoxic effects, which do not seem relevant to the CT participants	☐
		Sufficient data and no indication of risk	☐
	Comparator Investigational medicinal products/Auxiliary	*Non-clinical data summary*	☐
		Suspected/ demonstrated teratogenic or fetotoxic effects	☐
		Genotoxic	☐
		Insufficient data	☐
		Demonstrated embryo-fetotoxic effects, which do not seem relevant to the CT participants	☐
		Sufficient data and no indication of risk	☐
		Non-clinical data summary	☐
		Suspected/ demonstrated teratogenic or fetotoxic effects	☐

		Genotoxic	☐
	According to the recommendations related to contraception and pregnancy testing in clinical trials" the risk of teratogenicity/ fetotoxicity based on the non-clinical data is considered (please tick one)		☐ demonstrated/ suspected ☐ possible ☐ unlikely
	Comment:		
	4.7 Local tolerance		
	Do the submitted studies indicate a potential for local toxicity?		☐ YES ☐ NO ☐ NA
	Comments:		
	4.8 Other toxicity studies		
	Dedicated Study	***Toxicities identified***	***Findings***
	Phototoxicity	☐ YES ☐ NO ☐ NA	
	Tissue cross reactivity	☐ YES ☐ NO ☐ NA	
	Antigenicity	☐ YES ☐ NO ☐ NA	
	Immunotoxicity	☐ YES ☐ NO ☐ NA	
	Dependence	☐ YES ☐ NO ☐ NA	
	Metabolites	☐ YES ☐ NO ☐ NA	
	Impurities	☐ YES ☐ NO ☐ NA	
	Other	☐ YES ☐ NO ☐ NA	
	Comments:		
5.	***Additional Considerations***		
	5.1 First in Human Trials		
	Is the starting dose adequately justified?		☐ YES ☐ NO ☐ NA
	Are the dose steps adequately justified?		☐ YES ☐ NO ☐ NA
	Is the maximum dose adequately justified?		☐ YES ☐ NO ☐ NA
	Assessor's comment*:*		

ANNEX-IX: Template for Review of trial amendment

Rwanda Food and Drugs Authority

Nyarutarama Plaza, KG 9 Avenue
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QMS N°: FDISM/PVSM/FMT/007
Revision No: 01
Effective Date: 11/04/2023

Review of trial amendment

Date of the submission (cover letter)			
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Investigational Product storage Information	
Special Storage consideration	
Overall Conclusion of the CTAA Review	☐ **ACCEPTED** ☐ **ADDITIONAL DATA REQUESTED** ☐ **REJECTED**
Points to be communicated with the Clinical Trial Applicant: *Please copy all relevant information to be communicated to the CT applicant in the corresponding letter and save it accordingly*	
Clinical Trial Commitments (if any)	

REVIEW OF AMENDMENTS	
Type of Trial Amendment	☐ Clinical Protocol-Related Amendment ☐ Investigational Products Related Amendment
CURRENT ACCEPTED INFORMATION	**SUMMARY OF AMENDMENTS**
The rationale of the amendment (s)	
1. Clinical Protocol related amendments	
Does the amendment concern several trials involving the same IMP?	☐YES ☐ NO

	Reviewer's Comments:	
	Is the Amendment to the protocol? If Yes specify the changes made to the protocol	☐YES ☐ NO
	Reviewer's Comments:	
	Is an amendment to information in the CT application form or appended documents?	☐YES ☐ NO
	Reviewer's Comments:	
	Is this amendment concerns mainly urgent safety measures already implemented?	☐**YES** ☐ **NO**
	Do changes affect the safety or integrity of trial Participants?	☐**YES** ☐ **NO**
	Do changes affect the conduct or management of the trial	☐**YES** ☐ **NO**
	Do changes affect the interpretation of scientific documents/value of the trial	☐**YES** ☐ **NO**
	Does the change in Information on the temporary halt of trial?	☐**YES** ☐ **NO**
	If YES does the Treatment been stopped?	☐**YES** ☐ **NO**
	Reviewer's Comments: *(Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendments, Justification for a temporary halt of the trial, The proposed management of patients receiving treatment at time of the halt, The consequences of the temporary halt for the evaluation of the results and for overall risk-benefit assessment of the investigational medicinal product*)	
	Change or addition of principal investigator(s), coordinating investigator?	☐**YES** ☐ **NO**
	Change/addition of Clinical trial site(s)	☐**YES** ☐ **NO**
	Reviewer's Comments:	
	Have relevant supporting documents been provided? If No ask them.	☐**YES** ☐ **NO**
	Reviewer's Comments:	
2	**Amendment related to Investigational Products if applicable**	
	The change affect the entire manufacturing process of the investigational product	☐**YES** ☐ **NO**
	Reviewer's Comments:	
	The change involve the change manufacturing s the investigational product.	☐**YES** ☐ **NO**
	Reviewer's Comments:	

	Do changes in strength or dosage form of the investigational products?	☐**YES** ☐ **NO**
	Reviewer's Comments:	
	Do changes in extension of reduction in shelf life of Investigational products?	☐**YES** ☐ **NO**
	Reviewer's Comments:	
	Do changes on investigational products affect its quality, safety or efficacy?	☐**YES** ☐ **NO**
	Reviewer's Comments:	
	Other changes related investigational products	☐**YES** ☐ **NO**
	Reviewer's Comments:	
	Do relevant supporting documents related to amendments submitted? If NO request the PI/Sponsor to submit all necessary documents	☐**YES** ☐ **NO**
	Reviewer's Comments:	
	General Reviewer's Comments:	