African Vaccine Regulatory Forum (AVAREF)

CLINICAL ASSESSMENT

Study's full title	
Short title	
Protocol No.	
Version No.	
Investigational medical product	
Date of the review	
Reviewer's name	

Version	**Date**	**Comments**
Version 1	September 2018	Endorsed by Avaref's steering committee in Entebbe, Uganda,
Version 2	October 2019	To be tabled for adoption at the Avaref Assembly in Victoria Falls, Zimbabwe

General information for reviewers:

- Text provided in blue and in the footnotes is indicative and aims to highlight aspects that need to be taken into account during the assessment. It should be deleted prior to sending the final assessment to the sponsor
- 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
- The not applicable (NA) box should be checked off when the information is not required. A justification from the sponsor is expected in this case. The assessor is to comment on the acceptability of the information

1.1 Background information

1.1.1 Phase of the trial

Workspace:
Comments (if in disagreement with the study phase proposed):

1.1.2 Therapeutic condition

Workspace: **Brief** description of the disease:

1.1.3 Mechanism of action, drug class

Workspace: Add a **brief** description:

1.2 Status of development

Workspace: **Brief** discussion of clinical pharmacokinetic data, efficacy and safety data described in the IB[1] 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

[1] The IB provides the summary of all the clinical trials conducted prior to the one under review. The assessor can request the full study report, including appendices, if a more throughout review of the clinical data are deemed necessary.

Assessor's discussion on the clinical development:

1.3 Proposed clinical trial

1.3.1 Clinical trial Rationale

Is the rationale for the trial provided by the sponsor acceptable?	Yes ☐ No ☐
Workspace: • Consider what is new in this trial, the clinical relevance, and the medical need that the trial aims to address	
Comments:	

1.3.2 Primary objective(s) and endpoint(s)

List of primary objective(s):	
The primary objective(s) are clearly defined and measurable and are acceptable	Yes ☐ No ☐
List of primary endpoint(s):	
The primary endpoint(s) are acceptable	Yes ☐ No ☐
Workspace: • Consider if there are established primary endpoints for this type of study/indication, do they match the goals, are they validated?	
Comments:	

1.3.3 Secondary objective(s) and endpoint(s)

List of secondary objective(s):	
The secondary objective(s) are clearly defined and measurable and are acceptable	Yes ☐ No ☐

List of secondary endpoint(s):	
The secondary endpoint(s) are acceptable	Yes ☐ No ☐
Workspace:	
Comments:	

1.3.4 Study population as per the study protocol

Healthy volunteers/ patients	Healthy volunteers ☐ Participants ☐
Age range	Adults ☐ Children/adolescents ☐ Elderly ≥65 years ☐ Age group if children/adolescents proposed:
Gender	M ☐ F ☐
	Women of childbearing potential on contraception, provide numbers
	Women of childbearing potential not on contraception, provide numbers
Workspace:	
Comments:	

1.3.5 Inclusion criteria

List of inclusion criteria:	
The inclusion criteria are rationally defined, representative of the target population and are acceptable	Yes ☐ No ☐
Workspace: • Take also into consideration the gender and age allocation of participants, and determine whether a specific group is excluded or underrepresented	
Comments:	

1.3.6 Exclusion criteria

List of exclusion criteria:	
The exclusion criteria are rationally defined and in accordance with IMP/comparator's safety profile:	Yes ☐ No ☐
Workspace:	

• Check if a justification is provided in the event that a specific group is excluded or underrepresented • For registered products: consider the contraindications included in the SmPC for the investigational medical product, comparator, and auxiliary medical products
Comments:

1.3.7 Vulnerable populations and clinical trials in emergency situations

Vulnerable populations[2] are included in the study ☐ **If yes,** specify which population(s):	
The inclusion of vulnerable population(s) is **justifiable**	Yes ☐ No ☐ NA ☐
The **benefit/risk profile** is acceptable	Yes ☐ No ☐ NA ☐
For emergency clinical trials only: Does the trial provide clinically relevant direct benefit to the participants?	Yes ☐ No ☐ NA ☐
Workspace: • The inclusion of a vulnerable population is justifiable only if this information cannot be obtained from non-vulnerable populations • For incapacitated or minor participants, the trial should offer some direct benefit to them or to the population they represent	
Comments:	

1.3.8 Study plan and design

Is the proposed study plan and design acceptable?	Yes ☐ No ☐
Workspace: • **Brief** description of the study plan and design, and whenever possible, include a diagram/flow chart • Discuss the expected duration of the participants' participation and a description of the sequence and duration of all the clinical trial periods, including the follow-up	
Comments:	

[2] Pregnant and breast-feeding women, women of child bearing age not on contraception, incapacitated participants without decision making capacity, and/or incapacitated participants without decision making capacity

1.3.9 Study treatment

1.3.9.1 Investigational medical product(s) (IMP(s))

(Copy and repeat this section as necessary)

Summary of proposed use of the IMP in this trial:
Is the justification for the dose(s)/dose steps, dose rationale, route of administration, schedule, treatment duration, and dose modifications of the IMP acceptable? Yes ☐ No ☐ Other, comment ☐
Workspace: • Consider the dose(s)/dose steps, dose rationale, route of administration, schedule, treatment duration, and dose modifications
Comments:

1.3.9.2 Comparator IMP(s)/placebo/Auxiliary medical product(s)

(Copy and repeat this section as necessary)

Comparator IMP(s)

The study protocol proposes the use of a **comparator IMP** ☐
Brief information on the comparator: Include information on dose, route of administration, schedule, treatment duration and wash out period
The comparator is a standard therapy as per: • The SmPC ☐ • International or national guidelines[3] ☐ • Scientific publications[4] ☐
The use of the comparator is justified and is acceptable: Yes ☐ No ☐ Consider dose rationale, route of administration,

[3] Include a reference to the guidelines in the comment section

[4] Include the reference in the comment section

schedule, treatment duration, and dose modification(s)
Workspace:
Comments:

Placebo

The study protocol proposes the use of a **placebo** ☐
The use of a placebo controlled design is properly justified: Yes ☐ No ☐ Take for example cases when there is no proven intervention available or where the use of placebo is necessary to establish the efficacy or safety of an intervention and the patient receiving the placebo is not subject to any risk of serious or irreversible harm A lower degree of details (justification) is required for trials where the placebo group will also receive active treatment. Participants in the placebo arm should receive at least the standard of care
Workspace:
Comments:

Auxiliary medical product(s)

The study protocol proposes the use of an auxiliary medical product(s)[5] ☐
The use of auxiliary medical products in the trial is justified and acceptable: Yes ☐ No ☐ Inform the quality assessor if any auxiliary medical product used in the trial is not registered
Workspace:
Comments:

1.3.9.3 **Additional considerations for trials using a medical device**

The trial includes the investigation of a medical device(s)	Yes ☐ No ☐
The use and investigation of the medical device is considered acceptable [6,7]	Yes ☐ No ☐

[5] Those include background therapy, rescue medication, challenge agents, and/or medical products to assess endpoints

[6] For definitions and classification of medical devices see: WHO Global Model Regulatory Framework for Medical Devices including in vitro diagnostic medical devices 2017 - WHO Medical device technical series

Workspace:
Comments:

1.3.10 Safety: List of important safety risks associated with trial treatments (IMP/comparator/auxiliary medical products/medical devices)

Workspace: **Brief** description of the important safety risks associated with trial treatments identified in any previous clinical trials, and as outlined in the IB or SmPC, or from another source[8]
Comments:

1.3.11 Blinding and unblinding-clinical aspects (where applicable)

The procedure for emergency unbinding is described in the protocol and is acceptable:	Yes ☐ No ☐
In the case where a particular laboratory finding or a specific adverse reaction might reveal the treatment allocation, there are additional measures in place to protect the blinding:	Yes ☐ No ☐
Workspace:	
Comments:	

1.3.12 Contraception measures

Risk to the embryo and/or foetus[9]: Overall risk category Based on non-clinical and clinical data, the risk of teratogenicity/fetotoxicity in early pregnancy is: Demonstrated/suspected ☐ Possible ☐ Unlikely ☐ Consider the risk as possible if it's unknown
Are contraceptive measures adequately defined and acceptable? Yes ☐ No

[7] Also consider companion diagnostics and software

[8] For a list of important safety risks associated with the trial treatments identified in nonclinical studies consult the corresponding section in the nonclinical assessment

[9] For IMPs that **are not registered,** refer to the nonclinical assessment for IMP/comparator IMP/auxiliary medical products, as applicable. For IMPs that **are registered,** refer to the summary of product characteristics for IMP/comparator IMP/auxiliary medical products, as applicable

If No - tick appropriate box below and **provide comment**	☐
Method of contraception proposed for WOCBP in the study is insufficient or an effective method is listed as a highly effective method (e.g. double barrier)	☐
Contraception for male participants is required but is not included or is insufficient in the protocol	☐
Contraception after the end of treatment is not included in the protocol or the duration of this contraception is insufficient	☐
Pregnancy testing at screening is not included or there is an inappropriate interval from time of pregnancy test to start of treatment	☐
Insufficient frequency of pregnancy tests during the study (as per CTFG guidelines)	☐
Definition of WOCBP or postmenopausal woman is not included in the study protocol or is inadequate	☐
Other issue:	☐
Workspace:	
Comments:	

1.3.13 Discontinuation criteria for participants and stopping criteria

The protocol includes discontinuation criteria for participants from treatment or from the trial, and procedures to collect data from those who withdraw[10]	Yes ☐ No ☐
These criteria and procedures are considered acceptable[11]	Yes ☐ No ☐
Clinical trial termination criteria are included in the protocol and are acceptable	Yes ☐ No ☐
Workspace:	
Comments:	

1.3.14 Other concomitant therapy

A description of permitted medications is included in the study protocol and is acceptable[12]	Yes ☐ No ☐
A description of prohibited medications is included in the study protocol and is acceptable[13]	Yes ☐ No ☐

[10] Patients with disease progression or who are not responding to treatment should be withdrawn from the trial or otherwise justified

[11] Consider also discontinuation criteria for the IMPs including comparator and placebo for background therapy, and for vulnerable population

[12] Consider the contraindications listed in the SmPC/IB for the IMP(s)/comparator(s)/auxiliary medical products, medications with potential PK interactions, and any food or other lifestyle restrictions proposed

Workspace:
Comments:

1.3.15 Safety and Monitoring

1.3.15.1 Study procedures, visits and monitoring of participants, and follow up

Are the study procedures, study visits, monitoring of participants, risk minimization measures, and follow-up adequately described and acceptable? If No - tick the appropriate box and comment	Yes ☐ No ☐
The frequency of the study visits/monitoring is insufficient	☐
The relevant targets are not monitored[14]	☐
The proposed risk minimization measures and risk management guidelines (including monitoring, treatment modifications in case of toxicities) are not acceptable	☐
Risks associated with the study procedures, including diagnostic procedures, are unacceptable	☐
The follow-up period after the treatment is completed or after adverse reactions is insufficient	☐
Other issues:	☐
Workspace:	
Comments:	

1.3.15.2 Reference Safety Information

Reference Safety Information (RSI) is included in the SmPC or IB	SmPC ☐ IB ☐ **Version, Date and Section of IB:**
The document proposed as the RSI (SmPC or IB) is acceptable	Yes ☐ No ☐
The format of the RSI is acceptable (where IB is used)	Yes ☐ No ☐
The list of the proposed ARs declared as "expected" is acceptable (where IB is used)	Yes ☐ No ☐
Workspace:	
Comments:	

[13] Consider the contraindications listed in the SmPC/IB for the IMP(s)/comparator(s)/auxiliary medical products, medications with potential PK interactions, and any food or other lifestyle restrictions proposed
[14] Take for example AST/ALT, bilirubin, cases of Hy's law, etc for IMP(s) with known hepatotoxic effects

1.3.15.3 Data Safety Monitoring Committee (if applicable)

The trial has a data safety monitoring committee:	Yes ☐ No ☐
In cases where the trial has a DSMC, are the arrangements considered acceptable?	Yes ☐ No ☐
Workspace: • Elaborate if in disagreement with the sponsor with regards to the need for an independent DSMC, scope of the DSMC, frequency of the meetings, or other issues	
Comments:	

1.3.16 Definition of the end of the trial

A definition of the end of trial[15] is provided and acceptable?	Yes ☐ No ☐
Workspace:	
Comments:	

1.3.17 Biological samples used in the study (if applicable)

Are the procedures to collect, store, and future use of biological samples appropriately described?	Yes ☐ No ☐
Are these procedures acceptable?	Yes ☐ No ☐
Workspace:	
Comments:	

1.3.18 Data protection

The data protection policies as described in the protocol are **not** acceptable. **(Tick the appropriate box** and **comment)**	☐
Organisational and technical arrangements to avoid unauthorised access, disclosure, dissemination, alteration or loss of information and personal data processed are **insufficiently described or are unacceptable**	☐
Measures to ensure confidentiality of records and personal data of participants are **insufficiently described or are unacceptable**	☐
Measures that will be implemented in case of data security breach are **insufficiently described or are unacceptable**	☐
Other issues:	☐

[15] It is usually defined as the last patient last visit

Workspace:
Comments:

1.3.19 Recruitment and informed consent procedures

Recruitment and informed consent procedures, as described in the study protocol, are **not** acceptable and/or **not** in compliance with ethical requirements on the protection of participants in clinical trials and informed consent Consider specific requirements for vulnerable populations, eg incapacitated patients, minors, pregnant or breastfeeding women, clinical trials in emergency situations	☐
Workspace:	
Comments:	

1.4 Benefit/risk assessment

1.4.1 Benefit/risk assessment[16]

The protocol contains an acceptable evaluation of the anticipated benefits and risks of participating in the trial	Yes ☐ No ☐
Are the measures[17] proposed to address the known and potential risks of participating in the trial and to protect participants acceptable? **If No - tick the appropriate box** below and **provide a comment**	Yes ☐ No ☐
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	☐
Workspace: Elaborate if in disagreement with the sponsor's evaluation of the benefit/risk	
Comments on the benefit/risk:	

[16] Consider the benefit/risk of study treatment(s) including IMPs, placebo, active comparator, auxiliary medical products, study procedures including diagnostic procedures, and risks arising from stopping current therapy. Special consideration should be given to the participants that receive placebo

[17] Consider special requirements for vulnerable populations

1.5 Assessor's overall conclusions on the clinical part

The clinical aspects of the application are acceptable	☐
Supplementary information needs to be provided (refer to the list of requests for additional information)	☐
Workspace:	
Overall comment/ conclusion on the clinical assessment:	

1.5.1 Requests for additional information