African Vaccine Regulatory Forum (AVAREF)

NON-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:

- Summary boxes are provided in relevant sections and can be completed at the assessor's discretion. They intent to outline the studies submitted and describe key aspects of the results
- The not applicable (NA) box should be checked off when the studies are either not performed or not required. A justification from the sponsor is expected in this case. The assessor is to comment on the acceptability of the information
- 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
- 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

1.1 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

1.2 Pharmacology

1.2.1 Primary pharmacodynamics

Summary	
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 ☐
Workspace:	

Provide a brief outline of the invivo/invitro studies performed to evaluate primary pharmacodynamics and the results
Comments:

1.2.2 Secondary pharmacodynamics

Summary	
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 ☐
Workspace:	
Comments:	

1.2.3 Safety pharmacology[1]

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☐
Workspace:			
Comments:			

[1] In case of integrated safety pharmacology/repeat dose studies as per ICHS6, cross-reference to section 4.4.3 in the comment box below. The assessment can be described in this section to avoid duplication

1.2.4 Pharmacodynamic drug interactions

Summary

Have potential pharmacodynamics drug interactions been identified?	Yes☐ No☐
Workspace: Describe briefly any invitro/invivo studies performed and their results if any was performed	
Comments:	

1.3 Pharmacokinetics

1.3.1 Methods of analysis

Are the methods of analysis and their sensitivities adequate?	Yes☐ No☐ NA☐
Workspace:	
Comments:	

1.3.2 Absorption, distribution, metabolism & excretion

Summary

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☐
Workspace: 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 (toxicokinetics) is enough	
Comments:	

1.3.3 Pharmacokinetic drug interactions (enzymes, transporter, other)

Summary

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 ☐	
Workspace: Describe briefly the invitro/invivo studies performed and discuss the results		
Comments:		

1.3.4 Other pharmacokinetic studies (e.g. PK of metabolite, novel excipients, genomic integration and inadvertent germline transmission of gene transfer vectors)

Summary

Were other PK studies performed?	Yes ☐ No ☐ NA ☐
Do these studies identify concerns?	Yes ☐ No ☐ NA ☐
Workspace: Describe briefly any additional invitro/invivo studies performed and the results	
Comments:	

1.4 Toxicology

Summary

1.4.1 Animal species selection/study design

Toxicologically relevant animal species studied	Yes ☐ No ☐ NA ☐
The studied species show similar pharmacology to humans	Yes ☐ No ☐ NA ☐
The studied species show similar PK to humans	Yes ☐ No ☐ NA ☐
The studies were sufficiently well-designed	Yes ☐ No ☐ NA ☐
Workspace: 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	
Comments:	

1.4.2 Single dose toxicity

Summary

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 ☐
Workspace: Brief description of any studies performed. The results should be presented in the tables			
Comments:			

1.4.3 Repeat-dose toxicity

Summary

Study duration	**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 ☐
Does the duration of treatment support the proposed trial duration?	Yes ☐ No ☐ NA ☐
Workspace: Brief description of any studies performed. The results should be presented in the tables	
Comments:	

1.4.4 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 ☐
Workspace:		
Comments:		

1.4.5 Carcinogenicity

Summary

Do studies identify potential for carcinogenicity?	Yes ☐ No ☐ NA ☐
Do sufficient margins of exposure exist for planned clinical exposure?	Yes ☐ No ☐ NA ☐
Workspace:	

Add a brief description of the studies performed and the results
Comments:

1.4.6 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 development, including maternal function	Yes ☐ No ☐ NA ☐	
Do sufficient margins of exposure exist for planned clinical exposure? Yes ☐ No ☐ NA ☐		
Workspace: Add a brief description of the studies performed and the results		
Comments:		

1.4.6.1 Juvenile toxicity studies

Summary

The studies used 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 ☐

Workspace: Add a brief description of the studies performed and the results
Comments:

1.4.6.2 Other studies (including enhanced PPND studies)

Summary

The studies identified potential toxicities	Yes ☐ No ☐ NA ☐
Do sufficient margins of exposure exist for planned clinical exposure?	Yes ☐ No ☐ NA ☐
Workspace: Add a brief description of the ePPND studies performed in line with ICHS6(R1) and any additional invitro or invivo studies, and the results	
Comments:	

1.4.6.3 Recommendations for contraception measures

Non-clinical data summary

IMP	*(check off all that apply)* 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 IMP/ auxiliary MP	*(check off all that apply)* NA ☐ Suspected or demonstrated teratogenic or fetotoxic ☐

	Genotoxic ☐ Insufficient data ☐ Demonstrated embryo-fetotoxic effects, which do not seem relevant to the CT participants ☐ Sufficient data and no indication of risk ☐

WOCBP[2]/male partners of WOCBP are included in the proposed clinical trial	Yes ☐ No ☐
According to the guidance issued by the Clinical Trials Facilitation Group on "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 ☐
Workspace: The assessor's recommendations/comments in this section are intended to inform the clinical assessor in the completion of section 5.3.7.4 on the assessment of the protocol in relation to embryo-fetal risk minimization measures	
Comments:	

1.4.7 Local tolerance

Summary

Do the submitted studies indicate a potential for local toxicity?	Yes ☐ No ☐ NA ☐
Workspace: Add a brief summary of the studies performed and the results	
Comments:	

[2] women of childbearing potential

1.4.8 Other toxicity studies

Dedicated Study	Toxicities identified	Findings
Phototoxicity	Yes ☐ No ☐ NA ☐	
Tissue cross reactivity	Yes ☐ No ☐ NA ☐	
Antigenicity	Yes ☐ No ☐ NA ☐	
Immuno-toxicity	Yes ☐ No ☐ NA ☐	
Dependence	Yes ☐ No ☐ NA ☐	
Metabolites	Yes ☐ No ☐ NA ☐	
Impurities	Yes ☐ No ☐ NA ☐	
Effect on the HERC channels	Yes ☐ No ☐ NA ☐	
Other	Yes ☐ No ☐ NA ☐	
Workspace:		
Comments:		

1.5 Additional considerations

1.5.1 First-in human trials

Summary

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 ☐
Workspace: Describe the starting dose , dose steps, and maximum dose expected for	

first-in-human trials
Comments:

1.6 GLP aspects

Were all pivotal safety studies performed in line with the good laboratory practices (GLP) of the Organization for Economic Cooperation and Development? Were the studies performed in a country that is a member of OECD Mutual Acceptance of Data (MAD) for GLP?	Yes ☐ No ☐ Unknown ☐
Workspace:	
Comments:	

1.7 Assessor's overall conclusions on the non-clinical part

The non-clinical data provided are acceptable	☐
Supplementary information needs to be provided (refer to the list of requests for additional information)	☐
Overall comment/ conclusion on the non-clinical assessment[3]:	

1.7.1 Requests for additional information: non-clinical

[3] Are all nonclinical findings of clinical relevance considered by the sponsor in the overall benefit/risk assessment of the trial?