African Vaccine Regulatory Forum (AVAREF)

NON-CLINICAL ASSESSMENT

Study Full Title	
Short Title	
Protocol No.	
Version No.	
Study Drug	
Date of review	
Name of reviewers	

Summary boxes

NA box

Trials with more than one IMP

1.1. Introduction

Note for IMPs with MA

Note for previously assessed IMPs without MA

1.2. Pharmacology

1.2.1. Primary pharmacodynamics

Summary

These pharmacology studies provide support for 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:
Assessor's comment:

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:	
Assessor's comment:	

1.2.3. 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☐
Workspace:	
Assessor's comment:	

1.2.4. Pharmacodynamic drug interactions

Summary

Have potential pharmacodynamics drug interactions been identified? Yes☐ No☐
Workspace:
Assessor's comment:

1.3. Pharmacokinetics

1.3.1. Methods of analysis

Are the methods of analysis and their sensitivities adequate? Yes☐ No☐ NA☐
Workspace:
Assessor's comment:

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:	
Assessor's comment:	

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:		
Assessor's comment:		

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:	
Assessor's comment:	

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:	
Assessor's comment:	

1.4.2. Single dose toxicity

Summary

Species	**Dose/ Route**	**NO(A)EL/LOEL /MNTD** (*delete as required)*	**Major findings**

Were significant toxicities identified?			Yes ☐ No ☐ NA ☐
Do sufficient margins of exposure exist for planned clinical exposure?			Yes ☐ No ☐ NA ☐
Workspace:			
Assessor's comment:			

1.4.3. Repeat-dose toxicity

Summary

Study duration	**Species**	**Dose/ Route**	**NO(A)EL/LOEL /MNTD** (*delete as required)*	**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:				
Assessor's comment:				

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 indicated genotoxic potential? Yes ☐ No ☐ NA ☐		
Workspace:		
Assessor's comment:		

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:
Assessor's comment:

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:		
Assessor's comment:		

1.4.6.1. Juvenile toxicity studies

Summary

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 ☐
Workspace:	
Assessor's comment:	

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:	
Assessor's comment:	

1.4.6.3. Recommendations for contraception measures

Non-clinical data summary

IMP

(please all appropriate)

Suspected/ demonstrated teratogenic or fetotoxic effects ☐

Genotoxic ☐

Insufficient data ☐

Demonstrated embryo-fetotoxic effects but which do not seem to be relevant to the CT subjects ☐

Sufficient data and no indication of risk ☐

Comparator IMP/ auxiliary MP

(please all appropriate)

NA ☐

Suspected or demonstrated teratogenic or fetotoxic ☐

Genotoxic ☐

Insufficient data ☐

Demonstrated embryo-fetotoxic effects but which do not seem to be relevant to the CT subjects ☐

Sufficient data and no indication of risk ☐

WOCBP/male partners of WOCBP are included in the proposed clinical trial	Yes ☐ No ☐

According to the guidance "CTFG 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:	
Assessor's comment: ***Note***	

1.4.7. Local tolerance

Summary

Do the submitted studies indicate a potential for local toxicity? Yes ☐ No ☐ NA ☐
Workspace:
Assessor's comment:

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 ☐	
Immunotoxicity	Yes ☐ No ☐ NA ☐	
Dependence	Yes ☐ No ☐ NA ☐	
Metabolites	Yes ☐ No ☐ NA ☐	
Impurities	Yes ☐ No ☐ NA ☐	

Other	Yes ☐ No ☐ NA ☐	
Workspace:		
Assessor's comment:		

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:	
Assessor's comment:	

1.5.2. ATMPs

Summary

Are there any additional relevant concerns for this product?	Yes ☐ No ☐ NA ☐
Workspace:	
Assessor's comment:	

1.5.3.

1.6. Scientific advice/ PIP

Scientific advice/PIP advice relating to non-clinical development was received	Yes ☐ No ☐
Workspace:	
Assessor's comment:	

1.7. GLP aspects

Were all pivotal safety studies performed in line with OECD-GLP and performed in a country that is a member of OECD Mutual Acceptance of Data (MAD) for GLP?	Yes ☐ No ☐ Unknown ☐
Workspace:	
Assessor's comment:	

1.8. Assessor's Overall Conclusions on 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: *Note*	

1.9.

1.9.1. REQUESTS FOR ADDITIONAL INFORMATION: NON-CLINICAL (see also section 9)