4. NON-CLINICAL ASSESSMENT

Summary boxes

NA box

Trials with more than one IMP

4.1 Introduction

Note for IMPs with MA

Note for previously assessed IMPs without MA

Workspace:

Date

XXX is a YYY intended for the treatment of .

Protocol (Phase):

Primary objectives:

Secondary objectives:

Exploratory objectives:

Study design:

Dosing regimen:
IMP: max mg/kg per day for months

Dose justification:
For FIH, go to section 4.5.1

Population:
patients, male & female, adults & elderly
☐ Contraception/Pregnancy testing: Go to section 4.4.6.3
☐ Patients:

Clinical experience:

Regulatory status of the imp and of comparator:

SA ☐ Go to section 4.6

Provided version protocol=
Provided Version IB=
Provided Version IMPD=

Please address following key questions:

- *IMP - intended indication*
- *Study design*
- *Dosing regimen and treatment duration (IMP: max x mg/kg per day for x months)*
- *Dose justification (For FIH, go to section 4.5.1)*
- *Population - patients, male & female, adults & elderly*
    - *Contraception/Pregnancy testing: Go to section 4.4.6.3*
    - *Patients: please specify*
- *Clinical experience*
- *Regulatory status of the imp and of comparator:*
- *Scientific advice - Go to section 4.6*
- *Previously identified major issues/concerns that are relevant to the assessment of the non-clinical data for this clinical trials should be addressed. Same check is being done for clinical issues in the clinical assessment report:*
    - *Was there a previous refusal/recall/unresolved recommendation/condition etc.?*
    - *Are reasons for major issues resolved?*

Please, in case of identified issues, consider consulting the clinical team for input on:

- *Clinical rationale for (combination) therapy, if clinical data are provided in this context*
- *Inclusion and/or exclusion criteria*
- *Identification of potential overlapping toxicities for combination therapies and risk mitigation measures*
- *Data safety monitoring board*
- *Discontinuation and stopping criteria*
- *Study plan and design*
- *Safety monitoring*

Responsible team FIH: Non-clinical team (see also section 4.4.6.3)

Assessor's comment:

The applicant is requested to provide an adequate clinical trial protocol that is in compliance with current GCP guidance (ICH E6R2) and CTFG guidance (specifically "Recommendations related to contraception and pregnancy testing in clinical trials"). Reference is also made to the CTR (EU regulation No 536/2014), Annex I (application dossier for the initial application, section D. Protocol) (RFI).

The applicant provided an IB which is not following the standard template. As described in EU Regulation No 536/2014, the applicant is recommended to provide an IB prepared in accordance with international guidance. Non-clinical pharmacology and toxicology data shall be submitted in a logical structure, such as that of Module 4 of the ICH Common Technical Document format (RFI).

4.2 Pharmacology

4.2.1 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:	

Please address following key question:

- *Adequacy of inclusion criteria in line with primary pharmacology*

Please, in case of identified issues, consider consulting the clinical team for input on:

- *Clinical rationale for proof-of-concept for (combination) therapy*
- *Inclusion criteria in line with primary pharmacology*

4.2.2 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:	

Please address following key questions:

- *Adequacy of safety monitoring (type, extent, schedule, etc) in line with identified clinically relevant secondary pharmacology findings*
- *Adequacy of inclusion/exclusion criteria in line with identified clinically relevant secondary pharmacology findings*
- *Adequacy of discontinuation/stopping criteria in line with identified clinically relevant secondary pharmacology*

Please, in case of identified issues, consider consulting the clinical team for input on:

- *Inclusion and/or exclusion criteria*
- *Discontinuation and stopping criteria*
- *Safety monitoring*

4.2.3 Safety pharmacology

Summary

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:			

Please address following key questions:

- *Adequacy of safety monitoring (type, extent, schedule, etc) in line with identified clinically relevant safety pharmacology findings*
- *Adequacy of inclusion/exclusion criteria in line with identified clinically relevant safety pharmacology findings*
- *Adequacy of discontinuation/stopping criteria in line with identified clinically relevant toxicities*

Please, in case of identified issues, consider consulting the clinical team for input on:

- *Inclusion and/or exclusion criteria*
- *Discontinuation and stopping criteria*
- *Safety monitoring*

4.2.4 Pharmacodynamic drug interactions

Summary

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

Please, in case of identified issues related to pharmacodynamic interactions, consider consulting the clinical team for input.

4.3 Pharmacokinetics

4.3.1 Methods of analysis

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

Workspace:

Assessor's comment:

The applicant is recommended to provide information on the methods of analysis of the IMP (and/or its metabolites) in animal blood/plasma (validation and sensitivity). ***(recommendation for future clinical trials)***

4.3.2 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:

(For further clinical development) The applicant is invited to provide a detailed qualitative and quantitative overview of human metabolites and metabolites formed in test species, preferably in a tabulated format. (RFI or recommendation for future clinical trials)

4.3.3 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:		

Please, in case of identified issues related to pharmacokinetic interactions, consult the clinical team and the PK coordinator (or back-up) in case of questions about DDI.

Responsible team: clinical team

4.3.4 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:	

4.4 Toxicology

Summary

4.4.1 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:	

4.4.2 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:			

4.4.3 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:				

Please address following key questions:

- *Adequacy of safety monitoring (type, extent, schedule, etc) in line with identified clinically relevant toxicities*
- *Adequacy of inclusion/exclusion criteria in line with identified clinically relevant toxicities*
- *Adequacy of discontinuation/stopping criteria in line with identified clinically relevant toxicities*

Please, in case of identified issues, consider consulting the clinical team for input on:

- *Inclusion and/or exclusion criteria*
- *Discontinuation and stopping criteria*
- *Safety monitoring*

4.4.4 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:		

4.4.5 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:	

4.4.6 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:		

4.4.6.1 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:	

Please, in case of identified issues, consider consulting the clinical team for input on:

- *Inclusion and/or exclusion criteria*
- *Safety monitoring*

4.4.6.2 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:	

4.4.6.3 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:

A decision table can be used for the more complicated cases, see document 'Criteria to request pregnancy testing during treatment and after the last dose for oncology products':

Criteria for decision making toward pregnancy testing-AMEdit3.DOC

Assessor's comment: *Note*

For the definition of postmenopausal state and highly effective birth control methods used in the protocol, the applicant is referred to the "Recommendations related to contraception and pregnancy testing in clinical trials version 1.1 (21/09/2020)" of the Clinical trial facilitation group (CTFG) available at the HMA website:
https://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2020_09_HMA_CTFG_Contraception_guidance_Version_1.1_updated.pdf *(RFI)*

Please address following key questions:

- *Adequacy of inclusion/exclusion criteria for WOCBP, male patients with WOCBP partners*
- *Adequacy of contraceptive measures*
- *Adequacy of pregnancy testing requirements*
- *Adequacy of measures (if any) related to sperm or oocyte preservation*

Please consider the need for applying the criteria to request pregnancy testing during treatment and after the last dose for oncology products (https://gcloudbelgium.sharepoint.com/:w:/r/teams/GRP-FAMHP-CTRcollaboration-PregnancyTestingCriteriainOncoclinicaltrials/Shared%20Documents/Pregnancy%20Testing%20Criteria%20in%20Onco%20clinical%20trials/Criteria%20for%20decision%20making%20toward%20pregnancy%20testing-AMEdit3.DOC?d=w7231a272f4da47749037f6bcec3080d1&csf=1&web=1&e=V3OteM)

Please, consult the clinical team systematically for harmonization of considerations with regards to contraception and pregnancy testing.

Responsible Team: clinical team

4.4.7 Local tolerance

Summary

Do the submitted studies indicate a potential for local toxicity? Yes ☐ No ☐ NA ☐

Workspace:

Assessor's comment:

4.4.8 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:

In line with ICH M3 guideline and prior to phase 1, the Applicant should provide an initial assessment of the phototoxic potential of MP X based on the drug's photochemical properties and pharmacological/chemical class. If assessment of all the available data and the proposed clinical plan indicates a potential for a significant human phototoxicity risk, appropriate protective measures should be taken during outpatient clinical studies. If needed, the Applicant is advised to refer to the ICH S10 guideline (https://www.ich.org/products/guidelines/safety/safety-single/article/photosafety-evaluation-of-pharmaceuticals.html). (RFI)

OR

Before exposure of large numbers of subjects (Phase III), if appropriate, an experimental evaluation (nonclinical, in vitro or in vivo, or clinical) of phototoxic potential should be undertaken. (RFI)

4.5 Additional Considerations

4.5.1 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:	

Please address following key question:

- *Need for sentinel dosing*

Please, if involved and in case of identified issues, consider consulting the clinical team for input on:

- *starting dose, dose escalation, maximum dose*
- *Sentinel dosing*
- *Modelling of human exposure (PBPK, other)*

Non-clinical assessor should contact the PK coordinator (or back-up) in case there are PK issues related to the dose setting. Depending on classification in low/medium/high regulatory impact they will define the relevance of PK data on the decision-making process and the need to go further in assessment and contact a specialist in POP PK / modelling & simulation.

Responsible team FIH: non-clinical team

4.5.2 ATMPs

Summary

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

4.6 Scientific advice/ PIP

Scientific advice/PIP advice relating to non-clinical development was received	Yes ☐ No ☐

Workspace:

Assessor's comment:

Paediatric patients are included in this phase xx study, yet a PIP has not been submitted to EMA. According to the EU Paediatric regulation, a PIP application should be submitted as soon as possible after phase I clinical studies. The applicant is recommended to submit a PIP as soon as possible to seek feedback and approval from PDCO (Recommendation for future clinical trials).

Scientific Advice:

Focus on direct or indirect non-clinical related questions of a national or EMA scientific advice.

PIP:

- *Check compliance to the key binding elements in the agreed PIP if there is one, or deviations from important PDCO comments if the PIP procedure is still ongoing.*
- *In case of a paediatric trial and if PIP would have been expected at this stage in development, a comment is made only in the non-clinical report. Not needed by the clinical team as the PDCO alternate is part of the NC team.*

4.7 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:

CTFG and EU CTR NO 536/2014 documents on GLP in clinical trials

In accordance with EU Directives, applicants are reminded that all pivotal nonclinical studies need to be carried out in accordance with the principles of good laboratory practice (GLP). As applications for CTAs do not include individual study reports, Sponsors should include a statement on the GLP status of the studies within the IMPD, unless properly justified. A summary table should be provided specifying the details of each study and Sponsors should also indicate if in that period the facility was part of an accepted GLP monitoring programme. For more detailed information, see http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/QAs_document_on_GLP_-_2017.pdf

See also Q1.19 from the Q&A to the CTR: See Eudralex volume 10 (RFI)

4.8 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)	☐

Workspace:
Overall comment/ conclusion on the non-clinical assessment: *Note*

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

4.8.1.A PROPOSED LIST OF REQUESTS FOR ADDITIONAL INFORMATION BY RMS

Workspace (List of proposed RFI): 1. BExxx 2. BExxx