<Co>Rapporteur day <60\*><80> critical assessment report

\*in case of accelerated assessment

Clinical aspects

<Product name>

International non-proprietary name: <INN> or <Common name\*\*>

\*\*e.g. for vaccines and some ATMPs

<Pharmaceutical form and strength>

Procedure No. EMEA/H/C/<XXX>

Applicant:

|  |  |
| --- | --- |
| <CHMP>/<CAT> Rapporteur: |  |
| <CHMP>/<CAT> Co-rapporteur: |  |
| <CHMP coordinator(s)>  to be included only for CAT procedures |  |
| EMA PL: |  |
| Start of the procedure: |  |
| Date of this report: |  |
| Deadline for comments: |  |

Instructions to Applicants/Rapporteurs for use of this template

In the event that the **Applicant** agrees to pre-fill the factual sections of the template, guidance text for them is provided in blue.

The applicant is expected to pre-fill the factual sections of this template in an objective, data-driven way, without any bias or promotional intent.

Cross-references should be used to clearly indicate the origin of any information used in the report, such as the specific parts of the dossier (e.g. clinical overview, summary, study reports), references to the literature or other sources.

The use of tables/graphs/figures is encouraged; examples are given in the template and are to be used as appropriate. Tables taken from the dossier may also be included in the template. Footnotes should not be forgotten. Tables should be added as MS Word tables and not copy/pasted as pictures or from PDF.

Separate pages have been added in the template to include a list of abbreviations and references, to be completed when necessary.

It is recommended that the font used in the main text be Verdana, size 9.

Moreover, in general, the following aspect should be considered when filling in the template:

* For each main section of the assessment report for module 5, the report should describe the data submitted in accordance with Annex I of Directive 2001/83/EC. The types of studies addressed within each section should include all indents as listed in Annex I of Directive 2001/83/EC section 4.2.
* Justifications should be provided for waiving certain studies or for substituting them with publications.
* If data from publications is used, a direct link as well as clear referencing should be included allowing for clear identification of the publications. Consider the generation of a reference list if a substantial number of publications is used.
* If some aspects of development are to be included, please introduce the clinical development programme factually in view of the proposed indication and posology (indicate if there is a paediatric indication or development). State if the range of studies is in agreement with relevant EU/ICH guidelines.

Prior to the submission of the completed template via Eudralink, the Applicant is asked to **remove any Protected Personal Data in the metadata of the document, such as name of author etc**. The applicant is also asked to remove the blue guidance text only (not the green). See the instructions below.

The principle of the template is to make clear distinctions between the presentation of data (methodology and results) and the judgement (“Rapporteur’s comments”).

Guidance text for **(Co)Rapporteurs** is provided in green. If the Applicant has not agreed to pre-fill the factual sections, this will be done by the Rapporteur, and they can use the blue text as a reference.

In the cases where the Applicant has agreed to complete the factual sections of this report, it is expected that there should not be many cases of disagreements. However, Rapporteurs can choose to:

* Either amend the sections completed by the Applicant if they consider that the factual data has not been reported accurately.
* Or leave the applicant’s section as-is and comment on disagreements in the commenting boxes.

Specific assessment conclusions should in any case be included in the boxed sections of the report, not in the factual sections.

In general, the following aspects should be considered:

* The data submitted should be assessed based on the legal basis of the application, other legal/regulatory data requirements, applicable guidelines and other scientific criteria.
* The report should be sufficiently detailed to allow for secondary assessment by other CHMP/CAT experts.
* The report should assess salient findings and especially those deficiencies that justify the questions for the applicant. These questions will be listed only in the “CHMP AR/overview”.
* The report should also emphasise findings that need to be reflected in the SmPC.
* For each type of study, the report should distinguish between main (pivotal) and supportive data.
* The report should indicate if acceptable justifications have been provided for waiving the need to conduct certain studies, replacing original studies with literature data or when data submitted deviate from the legislation and guidelines requirements. If certain studies are only available as publications, it is important to clarify whether or not such studies are/are not of sufficient quality to allow an in-depth assessment of crucial data.
* In particular, for mixed or hybrid applications, the absence of any data for clinical trials, or the use of bibliographic references substituting in part or completely original data for the main studies (pivotal data) must be justified taking into account the legal basis of the Application.
* If data from publications is used in the context of the assessment, a clear referencing should be included allowing for clear identification of the publications. Consider generating a reference list if a substantial number of publications is used. If appropriate, ensure clear expression of the view on the content of a publication (e.g. if used not only as data reference but in the context of a discussion).

The list of clinical questions is to be included only in the CHMP AR/overview document. For reference please consider the following for the classification of the questions raised:

* “Major objections” preclude a recommendation for marketing authorisation. In principle, the major objection should start with a statement concerning the pivotal shortcoming, may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents.

Ideally, the objection should include a clarification as to what kind of response/action is expected from the applicant.

* “Other concerns” may affect the proposed conditions for marketing authorisation and product information. Other concerns should be resolved before approval; failure to do so may render the application un-approvable.

Note to the (Co)[Rapporteurs](https://www.ema.europa.eu/en/glossary/rapporteur): Assessment reports and comments should be circulated **VIA EUDRALINK**. Product Shared Mailbox: product.name-xxxx@ema.europa.eu and product initial MAA dedicated mailbox: MAAxxxx@ema.europa.eu (xxxx refers to the product number EMA/H/C/xxxx) should always be copied.

**How to remove the guidance text:**

Click on Ctrl-Alt-Shift-S to view the “styles” window. Select “Guidance text – Applicant” or “Guidance text – Rapps” and “Guidance text – black” and click on the icon on the right, chose “Select all XXX instances”, press the “Delete” key on the keyboard.

**Administrative information**

To be completed by the applicant (if they agreed to pre-fill the template), or the Rapporteur (in case applicant has not agreed to pre-fill)

|  |  |
| --- | --- |
| Product data |  |
| Product name |  |
| INN or Common Name |  |
| EMA Product Number |  |
| ATC code |  |
| Pharmaceutical form(s) and strength (s) |  |
| Route of administration |  |
| Proposed indication |  |
| Orphan designation | <Yes/No> (if yes, include ODD number) |
| PRIME scheme | <Yes/No> |

To be completed by the Rapporteurs

**EMA to redact ahead to circulation to company/ies**

|  |  |  |
| --- | --- | --- |
| Assessment team |  |  |
| <CHMP><CAT> Rapporteur | Rapporteur | Include name, email address and phone number for each row |
|  | Contact person |  |
|  | Quality |  |
|  | Non-clinical |  |
|  | Clinical |  |
| <CHMP><CAT> Co-Rapporteur | Co-Rapporteur |  |
|  | Contact person |  |
|  | Quality |  |
|  | Non-clinical |  |
|  | Clinical |  |
| EMA Product Lead | - |  |

To be completed by the assessment team:

|  |
| --- |
| **Declarations**  The assessment team should tick one or other of the 2 boxes below:  The (co)Rapporteur and/or the assessor confirm(s) that this assessment **does not** include non‑public proprietary information (with the exception of data provided by the applicant), including commercially confidential information provided by a third party (e.g. ASMF, information shared by other competent authorities or organisations, reference to on-going assessments, development plans etc), irrespective from which entity was received.  The (co)Rapporteur and/or the assessor confirm(s) that this report **does** include non-public information (as described above), but all relevant paragraphs containing confidential information have been **highlighted in red**, so that they can be removed before sharing the document with the applicant or other parties. |

Table of contents

[1. Introduction 9](#_Toc140850945)

[1.1. Type of application 9](#_Toc140850946)

[1.2. Therapeutic context 10](#_Toc140850947)

[1.3. Aspects of development 11](#_Toc140850948)

[1.3.1. Scientific advice/Protocol assistance 11](#_Toc140850949)

[1.4. Description of the product 11](#_Toc140850950)

[2. Clinical pharmacology 12](#_Toc140850951)

[2.1. Methods 12](#_Toc140850952)

[2.1.1. Bioanalytical methods 12](#_Toc140850953)

[2.1.2. Pharmacokinetic data analysis 13](#_Toc140850954)

[2.1.3. Evaluation and Qualification of Models 14](#_Toc140850955)

[2.2. Pharmacokinetics 15](#_Toc140850956)

[2.2.1. Absorption 15](#_Toc140850957)

[2.2.2. Distribution 18](#_Toc140850958)

[2.2.3. Elimination 19](#_Toc140850959)

[2.2.4. Metabolism 21](#_Toc140850960)

[2.2.5. Dose proportionality and time dependency 24](#_Toc140850961)

[2.2.6. Intra- and inter-individual variability 25](#_Toc140850962)

[2.2.7. Pharmacokinetics in the target population 26](#_Toc140850963)

[2.2.8. Special populations 27](#_Toc140850964)

[2.2.9. Pharmacokinetic interactions studies 33](#_Toc140850965)

[2.2.10. Exposure relevant for safety evaluation 37](#_Toc140850966)

[2.3. Pharmacodynamics 37](#_Toc140850967)

[2.3.1. Mechanism of action 37](#_Toc140850968)

[2.3.2. Primary pharmacology 38](#_Toc140850969)

[2.3.3. Secondary pharmacology 39](#_Toc140850970)

[2.3.4. Pharmacodynamic interactions with other medicinal products or substances 40](#_Toc140850971)

[2.3.5. Genetic differences in PD response 40](#_Toc140850972)

[2.3.6. <Immunological events> 41](#_Toc140850973)

[2.4. Pharmacokinetics-Pharmacodynamics (PK/PD) 42](#_Toc140850974)

[2.4.1. Relationship between plasma concentration and effect and safety 42](#_Toc140850975)

[2.4.2. Evaluation and Qualification of PK/PD Models 42](#_Toc140850976)

[2.5. Dose justification 43](#_Toc140850977)

[2.6. Assessor’s overall conclusions on the Clinical Pharmacology package 44](#_Toc140850978)

[2.6.1. Discussion 44](#_Toc140850979)

[2.6.2. Product information 45](#_Toc140850980)

[2.6.3. Conclusions 46](#_Toc140850981)

[3. Clinical efficacy 47](#_Toc140850982)

[3.1. Clinical development 47](#_Toc140850983)

[3.2. Dose response study(ies) 48](#_Toc140850984)

[3.3. Main study(ies) 48](#_Toc140850985)

[*3.3.1.* <Study #1 identifier> <Study title> 49](#_Toc140850986)

[3.3.2. <Study #2 identifier> 61](#_Toc140850987)

[3.4. Clinical studies/subgroup analysis in special populations 61](#_Toc140850988)

[3.5. In vitro biomarker test for patient selection for efficacy 62](#_Toc140850989)

[3.6. Analysis performed across trials (pooled analyses AND meta-analysis) 63](#_Toc140850990)

[3.7. Supportive study(ies) 63](#_Toc140850991)

[3.8. <Patient><and><healthcare provider> engagement> 64](#_Toc140850992)

[3.9. GCP aspects 65](#_Toc140850993)

[3.10. Overall Rapporteur assessment of clinical efficacy 67](#_Toc140850994)

[3.10.1. Discussion 67](#_Toc140850995)

[3.10.2. Product information 69](#_Toc140850996)

[3.10.3. <<Patient><and><healthcare provider> engagement> 70](#_Toc140850997)

[3.10.4. Conclusions: 70](#_Toc140850998)

[4. Clinical safety 71](#_Toc140850999)

[4.1. Safety data collection 71](#_Toc140851000)

[4.2. Patient exposure 71](#_Toc140851001)

[4.3. Adverse events 72](#_Toc140851002)

[4.3.1. Adverse drug reactions 73](#_Toc140851003)

[4.4. AEs of special interest, serious adverse events and deaths, other significant events 74](#_Toc140851004)

[4.4.1. ADRs of special interest, serious ADRs and deaths causally related to the medicinal product. 74](#_Toc140851005)

[4.5. Discontinuation due to adverse events 75](#_Toc140851006)

[4.6. Safety in special populations 76](#_Toc140851007)

[4.6.1. ADRs in special populations 78](#_Toc140851008)

[4.7. Safety related to drug-drug interactions and other interactions 78](#_Toc140851009)

[4.8. Laboratory and other findings 79](#_Toc140851010)

[4.9. Post marketing experience 80](#_Toc140851011)

[4.10. Adverse drug reactions in SmPC 80](#_Toc140851012)

[4.11. <In vitro biomarker test for patient selection for safety> 81](#_Toc140851013)

[4.12. Overall Rapporteur assessment of clinical safety 82](#_Toc140851014)

[4.12.1. Discussion 82](#_Toc140851015)

[4.12.2. Product information 84](#_Toc140851016)

[4.12.3. Conclusion 84](#_Toc140851017)

[5. Risk management plan 85](#_Toc140851018)

[5.1. Summary of safety concerns 85](#_Toc140851019)

[6. Pharmacovigilance system 87](#_Toc140851020)

[7. List of references 88](#_Toc140851021)

[8. Annex I (please delete when report finalised) 89](#_Toc140851022)

[8.1. Examples of tables for baseline data 89](#_Toc140851023)

List of abbreviations

To be completed by the applicant (if they agreed to pre-fill the template).

Rapporteurs to add to applicant’s list if needed, or to complete fully if the applicant has not agreed to pre-fill the template.

|  |  |
| --- | --- |
|  |  |
|  |  |
|  |  |
|  |  |
|  |  |

1. Introduction
   1. Type of application

Indicate the type of marketing authorisation application (reference to the legal basis of the application); complete/abridged; whether for conditional approval or under exceptional circumstances. Also indicate whether accelerated assessment was applied for and granted or not granted.

|  |  |
| --- | --- |
| Eligibility to the Centralised Procedure | Only choose 1 and delete the rest  <Article 3(1) and point <1> <3> <4> of Annex of Regulation (EC) No 726/2004.>  <Article 3 (2) <(a)> <(b)> of Regulation (EC) No 726/2004.>  <Article 28 of Regulation (EC) No 1901/2006.>  <Paediatric Use Marketing Authorisation in accordance with Article 30 of Regulation (EC) No 1901/2006, through the centralised procedure under Article 31 of Regulation (EC) No 1901/2006.>  <Article 58 of (EC) No Regulation 726/2004 for a scientific opinion in the context of cooperation with the World Health Organisation.> |
| Legal basis | Only choose 1 and delete the rest  <Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.>  <Article 10(a) of Directive 2001/83/EC, as amended – relating to applications relying on well‑established medicinal use supported by bibliographic literature.>  <Article 10(b) of Directive 2001/83/EC, as amended – relating to applications for fixed combination products.>  <Article 10(c) of Directive 2001/83/EC, as amended – relating to informed consent from a marketing authorisation holder for an authorised medicinal product. >  <Article 10(1)> of Directive 2001/83/EC, as amended – relating to applications for generic medicinal product.>  <Article 10(3)> of Directive 2001/83/EC, as amended– relating to applications for hybrid medicinal product.>  <Article 10(4) of Directive 2001/83/EC, as amended – relating to applications for a biosimilar medicinal product.>  <Article 58 of Regulation (EC) No 726/2004, - complete and independent application, by analogy to Article 8(3) of Directive 2001/83/EC.> |
| New Active Substance status claim | The applicant indicates that <INN/common name> is considered to be a <new><known> active substance. |
| Conditional marketing authorisation or authorisation under exceptional circumstances | <Not applicable> <The applicant is applying for a <conditional marketing authorisation><marketing authorisation under exceptional circumstances>.> |
| Accelerated assessment | <Not applicable> <The applicant submitted a request for accelerated assessment for <product name> on <date>. The application was <approved> <rejected> by CHMP at its meeting on <date>.> |

* 1. Therapeutic context

This section should be 1-3 pages in total length. It can be based on eCTD section 2.5.6.1. A thorough summary of the literature is not expected in this document. In some cases (e.g., for less-well known or rare diseases), more information may be useful to help establish the therapeutic context relevant to the product under review. References for more detailed information can be provided.

Provide background on the medical condition that is necessary to understand the therapeutic context of this application or is otherwise relevant to the review. This section can be abbreviated if the condition is well-recognized. A good background typically includes the following:

* Disease definition and important clinical characteristics
* Natural history of the condition, in particular, whether it generally progresses or remits and relapses, and whether there are subtypes with different patterns
* Major signs and symptoms, including their frequency, severity, and how they vary with disease severity, stage, or duration of illness
* Population affected (e.g., demographic groups, geographic and cultural considerations)
* Diagnostic criteria and methods used in clinical practice
* Incidence and prevalence of the condition, including rates of diagnosis, severity, mortality, and morbidity. Note any important variations across patient demographics or subpopulations.
* The impact the condition has on patients’ daily living (e.g., specific limitations, health-related quality of life issues), across the spectrum of severity. Consider the patients’ perspective about the impact of the condition, when known.
* Societal or global public health implications of the condition, if relevant (e.g., control and prevention, loss of productivity, etc.)
* Areas of uncertainty or limitations in understanding of the condition or its impacts.

Provide a succinct overview of therapies currently used in the EU to treat or prevent the condition in the claimed indication. If relevant, comment on any differences between standard of care in different regions, which may have impacted the choice of comparator in a global development programme. It should indicate how well these treatment options meet the medical needs of the patient population in the EU and how the treatment armamentarium could be enhanced in terms of the benefit, safety, and tolerability of treatments.

If relevant, briefly describe other treatments used for the indication, such as drugs used off-label (only if supported by strong evidence), non-prescription drugs, medical and surgical procedures, and non-drug therapies such as diet modifications and physical therapy.

<Text>

* 1. Aspects of development

Briefly summarise the clinical development programme in view of the (proposed) indication and posology. This section should take 1-2 pages at most, with all the detail expected later on in this document. It can be based on eCTD section 2.5.1.

Indicate the availability of development in other special populations such as in elderly, pregnant or lactating women, in males/females and ethnic minorities.

<Text>

* + 1. Scientific advice/Protocol assistance

Briefly describe the relevant scientific advice/protocol assistance received in the EU in relation to the development programme for the product. The focus should be on EMA scientific advice. Please keep it to a very brief summary of the main agreed aspects.

If the proposed indication includes paediatrics, indicate whether a Paediatric Investigation Plan (with or without deferral) or a product-specific waiver has been agreed with the PDCO, or whether a class waiver applies. Briefly summarise the conditions and principal requirements of the paediatric investigation plan with regards to clinical aspects.

If the development programme has diverted from the received advice, please briefly describe the reasons. Extensive explanations can be left for the eCTD, please limit the explanation to factual elements.

<Text>

* 1. Description of the product

Briefly describe the product being submitted. Mention the mechanism of action and whether it is already approved for use in any market. State the proposed indication and posology.

This section should be extremely brief and consist for the most part of the proposed SmPC sections 4.1 and 4.2.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  (Co)-Rapporteurs: if you consider the summary provided by the applicant to be factually incorrect (or that key information was omitted), please make a comment and describe the disagreement in this box.  <No comments><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

1. Clinical pharmacology

Please complete section 2 and subheadings of this report based on eCTD modules 2.7.1 and 2.7.2. Include the completion of template tables as reported below, without changes to the format. Use of additional tables for reporting data is also encouraged in any of the subheadings. Avoid repetition of the same data between text and tables.

For (Co)-Rapporteurs: if a separate PK assessment report is used, please copy/paste the applicant’s position from the sections below as needed.

Note: a specific, separate template for biosimilars is planned to be developed. Until that is available, please adapt the sections below as required.

Please complete the table below based on the information generally provided in eCTD section 2.7.2.1. Where appropriate, the chirality (whether a pure isomer is used or a mixture) of the substance should be mentioned.

Table 1: Phase 1 studies

If necessary, include also a list of studies without PK sampling (efficacy & safety), in cases where PK bridging will be applied.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study identifier | Study design | Population  (incl number of subjects, healthy vs patient and gender ratio) | Dosing regimen | Main PK parameters |
|  |  |  |  |  |
|  |  |  |  |  |

As for section 2.7.2.1 of the eCTD, provide a very high level (1 page max) summary of the clinical pharmacology programme that supports this application.

<Text>

* 1. Methods
     1. Bioanalytical methods

As for section 2.7.1 of the eCTD, provide a brief description of the analytical methods used, emphasising the performance characteristics of assay validation and quality control. In case of several analytical methods, a description of the validation should focus on the methods used for the most important clinical studies and should preferably be summarised in a table for each method. A table showing which method was used for which clinical study should also be provided.

Incurred sample reanalysis and cross-validation should also be addressed.

Add/remove the subsections below as required.

* + - 1. Pharmacokinetics

<Text>

* + - 1. PD biomarkers

<Text>

* + - 1. Immunogenicity

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  The compliance of the validation (pre-study and in-run) of the analytical methods with the current relevant guideline should be commented on. The same applies when other drugs (generally used in the DDI investigation) are part of the PK data package.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Pharmacokinetic data analysis

Please provide the following information: PK data analysis method and statistical methodology (PK parameters, non-compartmental procedure, software, CI and acceptance range (if relevant), etc.).

When non-compartmental (NCA) and modelled approaches are used, it is expected that both approaches concur. Any significant divergence should be reported and commented on. The comparison (when possible) of the PK parameters is a means to achieve that.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Are the methods used appropriately? Is any divergence suitably justified?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Evaluation and qualification of models

This section should only describe the models used and their qualifications; results should not be reported here but should be placed in the appropriate sections. Similarly, the result sections should not include descriptions of the models but should cross-refer to this section.

It is important that the main purpose of the model analysis should be clearly stated. Please provide population PK analysis, physiologically based pharmacokinetic (PBPK) modelling, regression models, and methods (e.g. model development, base model, covariate analysis, final model parameters, etc).

Any exclusion of data from analyses should be clearly justified. The strategy followed for the model development and model selection should be summarised with regard to the parsimony and plausibility of the model. The covariate model development approach should be described.

The performances of the model should be presented and discussed. This should include precision of the estimates and prediction-corrected visual predictive checks (pcVPCs) as well as any other model diagnostics which are important for understanding the overall model performance. For more detailed guidance on what to include, reference is made to the [EMA guideline on “Reporting the results of population pharmacokinetic analyses (CHMP/EWP/185590/06)”](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-reporting-results-population-pharmacokinetic-analyses_en.pdf) and “[Guideline on the reporting of physiologically based pharmacokinetic (PBPK) modelling and simulation” (EMA/CHMP/458101/2016)](https://www.ema.europa.eu/en/reporting-physiologically-based-pharmacokinetic-pbpk-modelling-simulation-scientific-guideline).

In order to avoid repetition, the reporting of the modelling work should be summarised and only a brief description of the modelling work (e.g. dataset, strategy of model development, description of the final model and data regarding its qualification, including Goodness-of-Fit and prediction performances, deviation from the analysis plan) should be reported here. Several findings described in the current section may be relevant also for other sections of the report, such as results from the covariates analysis related to e.g. healthy subjects versus patients and intrinsic and extrinsic factors should also be reported and discussed in the appropriate sections (such as target and special populations).

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  The evaluation and/or qualification of a model depend on the intended purpose and the regulatory impact which is directly linked to the risk to the patient in case the modelling predictions or assumptions lead to erroneous regulatory decisions. For requirements on PopPK and PBPK, reference can be made to the relevant guidelines.  Assess the validity of the model for use for the intended purpose, including modelling assumptions. Discuss uncertainties in model input and output.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Pharmacokinetics

Sections 2.2.1 to 2.2.4 (with the exception of section 2.2.1.2) are not applicable for biosimilars. Please state “Not applicable”.

* + 1. Absorption

Briefly summarise data from CTD module 5.3.1 to 5.3.3 if appropriate; studies are inserted here and tabulated whenever possible (e.g. rate and extent of absorption, involvement of active transport proteins in absorption).

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...).  For oral route, if no data is available with IV route, did the applicant perform a mass-balance study, or justify why one is not needed?  Conclude on involvement of transport proteins in the absorption and BCS classification. Discuss any non-linearity in absorption and potential pH dependency in solubility/absorption.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Bioavailability

Briefly summarise data from CTD module 5.3.1.1 - reports on Biopharmaceutical studies. Present both absolute and relative bioavailability.

For oral route, if no data is available with IV route, the lack of absolute bioavailability data should be discussed.

For oral route, the available data for the biopharmaceutical classification system (BCS) classification should be outlined and a statement regarding the BCS classification should be made.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  If absolute bioavailability is unknown, discuss the extent of absorption based on in vitro and other in vivo data (mass-balance, food effect study etc.)  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Bioequivalence

As for eCTD section 5.3.1.2, include data from bioequivalence studies between formulations used in pivotal clinical studies and the final formulation to be marketed. Other bioequivalence studies may be briefly presented. The level of detail needed depends on the importance of the data obtained with the specific formulation, but the focus should be on the final formulation to be marketed.

For clarity’s sake, it is very helpful to report (in a tabulated format) all the formulations used in PK development, i.e. in different phases: 1, 2 & 3. Such presentation will inform the need for bioequivalence demonstration (by the means of clinical studies or valid waiver) to bridge and elicit the compilation of the data from all studies.

For biological or biotechnology products this part should also cross-refer to non-clinical and functional assays.

Comparative PK studies designed to demonstrate equivalence between a similar biological medicinal product and the reference product with regard to key PK parameters are an essential part of the comparability exercise. Specific considerations related to the inherent characteristics of proteins are described in the [“Guideline on clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004)”](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-pharmacokinetics-therapeutic-proteins_en.pdf).

The reference product (used in clinical trials) should be indicated, and it should be clear if the reference product is authorised in the EU.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Influence of food

As per section 5.3.1.1 of the eCTD, provide food interactions studies data that represent the phase III and marketing formulation and support the proposed recommendations in the posology section of the SmPC. Please describe recommendations used in pivotal Phase III trials.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Discuss if the timing of intake in relation to food has been sufficiently evaluated and if proposed labelling recommendations regarding intake concerning food intake are appropriate.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Distribution

As per section 5.3.3 of the eCTD, provide data on the volume of distribution from studies in target population or PopPK, in vitro and ex vivo protein binding of parent drug and pharmacologically active metabolites. Provide the concentration range used in in vitro protein binding studies. Is protein binding independent of concentration? Discuss blood/plasma ratio, if available, data regarding concentration of parent drug and pharmacologically active metabolites in tissues and other body fluids, e.g. cerebrospinal fluid.

If estimations of the volume of distribution are available from non‑compartmental analysis (NCA) and Modelled approaches, their concurrence should be checked. Any significant divergence should be explained. If extreme estimates are obtained, an explanation of their physiological significance should be attempted.

For drugs exhibiting (very) high affinity to plasma proteins, the protein involved should be identified and information regarding the saturation of such binding under therapeutic concentrations should be provided.

<Text>

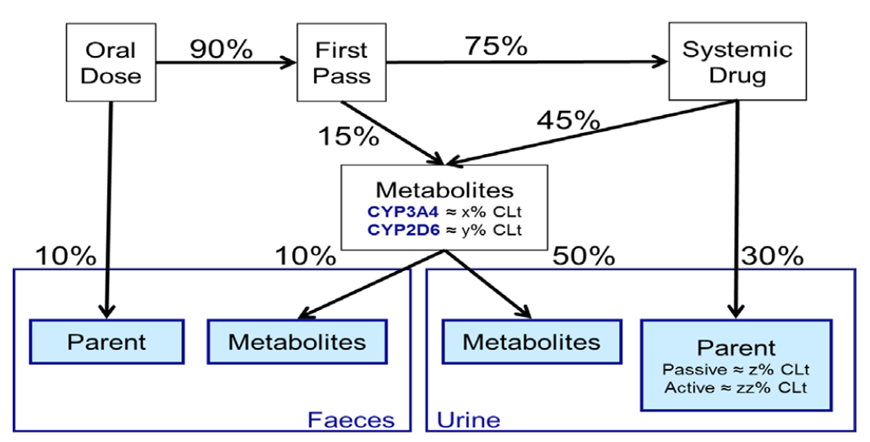
|  |
| --- |
| (Co)-Rapporteur’s comments:  Have the methods used for the investigation of in vitro binding to plasma proteins been described and validated? Is the concentration range appropriate in relation to clinically relevant exposures?  Discuss the relevance of the data provided.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Elimination

As per section 5.3.3 of the eCTD, please describe the main pathways of elimination (metabolism, excretion unchanged renally and biliary), clearance, half-life, as well as information on any potential accumulation.

Please include a figure such as the following or adapt when relevant (may not be relevant for biological medicinal products):

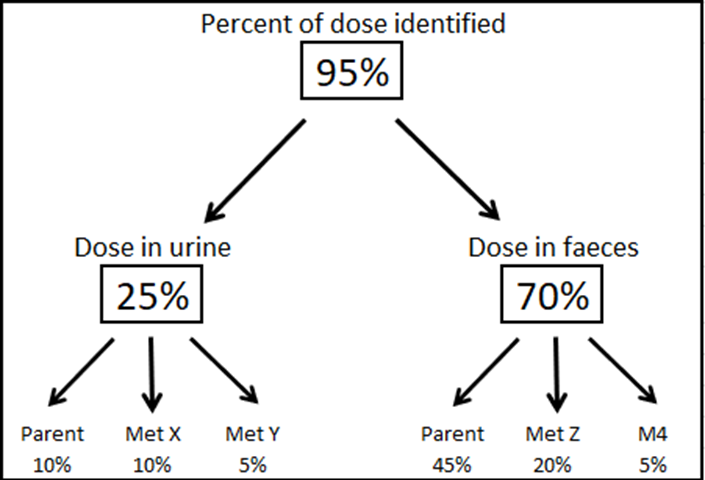
Figure 1: Elimination pathways



<Text>

When available, describe the design of the mass balance study(ies) and provide data on excretion of radioactivity. A figure such as the following is helpful.

Figure 2: Mass balance studies



<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Conclude on the clinical relevance of the formulation, dose (and duration) used in the mass balance study. Is the recovery in the mass balance study sufficient? Discuss the recovery and how much of the dose has been structurally identified in excreta in relation to guideline requirements.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Metabolism

As per section 5.3.3 of the eCTD, provide data on identification of metabolites, metabolic routes, enzymes involved in metabolism, extent of metabolism and proposed metabolism schedule. Any potential human specific metabolites?

Specify which metabolites are major according to the definition in the [“Guideline on the investigation of drug interactions (CPMP/EWP/560/95/Rev. 1 Corr. 2\*\*)”](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-drug-interactions-revision-1_en.pdf). Is there contribution of metabolites to efficacy and/or safety?

If an active moiety is used, this should be described and justified (e.g. protein binding, potency, molecular weight, etc). Cross-refer to the interaction section for the confirmation of the elimination route.

All in vitro data relevant to metabolism should be reported here, irrespective of the origin of the materials used. Please do not duplicate in the non‑clinical report.

Characterisation of radioactivity in plasma.

The AUC and half-life of parent drug and metabolites in relation to total drug related exposure (radioactivity in the mass-balance study). Estimation of how much of the AUC of radioactive material has been structurally identified.

A figure of plasma concentration-time profile of radioactivity and active substance can be given here. Provide terminal half-life of radioactivity.

Subheadings could be added as needed to structure the data.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Comment on the plausibility of the elimination pathway as presented by the applicant.  Conclude on which metabolites may be considered as “major” (contributing to ≥10% of total drug related exposure) and whether other unknown “major metabolites” are possible.  Are the estimations of the contribution of metabolites to efficacy and safety based on unbound exposure and pharmacological activity data, if possible, in combination with distribution characteristics to target tissue(s)?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Inter-conversion

Relevant for chiral products. Please address the possibility of inter‑conversion in vivo. Lack of stereoselective metabolism in the chiral centre in man and/or in non-clinical species or the absence of clinical consequences of inter-conversion should be justified. Please state if not applicable.

<Not applicable><Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Discuss the possible clinical consequences of inter-conversion and whether the applicant has adequately assessed the risk.  Consider the need for a chiral analysis method. For chiral substances where the enantiomers exhibit different PK and PD, a chiral analysis method and evaluation of the PK for the separate enantiomers may be needed.  <Not applicable><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <Not applicable><None><Text> |

* + - 1. Pharmacokinetics of metabolites

As per eCTD section 5.3.3, please include pharmacokinetic information available for active metabolites, and if available, also for inactive metabolites. Data for active metabolites with a large contribution to activity, and when relevant other metabolites, should be given in each relevant section of the assessment report.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Is any of the information provided about metabolites of concern? Any additional investigations needed?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Consequences of possible genetic polymorphism

As per eCTD section 5.3.3, include an evaluation of consequences if polymorphically expressed enzymes (e.g. CYP2D6, CYP2C19, N-acetyl transferase) are involved in the metabolism. A discussion of the potential influence in the inclusion and exclusion criteria of the patient population in the pivotal clinical trials should be also included.

Based on the elimination pattern, state on the need of specific investigations in rapid slow metabolizer and a subsequent dose adjustment. Discuss also on the need and practicability of genotyping and/or phenotyping of patients prior to treatment.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Discuss how well the SmPC (sections 4.2, 4.3, 4.4, 4.5 etc.) describes whether the information is relevant for a pharmacogenetic subpopulation.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Dose proportionality and time dependency
       1. Dose proportionality

As per eCTD section 5.3.3, provide information on dose proportionality after a single dose and at steady state. Describe whether or not the PK of the product is linear.

Describe the reason for any non-linearity: saturation of elimination, transport proteins, absorption, limited solubility, concentration dependent protein binding. Describe the consequences of the non-linearity, e.g. for dosing recommendations and the design of interaction studies.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Discuss the reason and the consequences for any non-linearity. Are the proposed dosing recommendations adequate? Have interaction studies been designed appropriately?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Time dependency

Provide data on systemic exposure after single and multiple dose administration of the therapeutic dose and evaluation of time dependency. When relevant, add information regarding the impact of anti-drug antibodies (ADAs) on PK (if required, use a separate heading).

Any accumulation after repeated dose should be described, and its clinical consequences should be discussed.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  If PK is time dependent, discuss reason and potential consequences (e.g. for dosing and drug-drug interactions).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Intra- and inter-individual variability

Provide data on intra- and inter-individual variability in pharmacokinetic parameters, preferably in the target population. If population pharmacokinetic analyses are available, data on intra- and inter- individual variability can be taken from these analyses. If the variability is high, sources of variability could be discussed.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Discuss whether intra- and inter-individual variability are sufficiently addressed in the posology determination.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Pharmacokinetics in the target population

Provide available PK data of parent compound and pharmacologically active metabolites in the target population with special emphasis on differences from healthy volunteers including variability in patients. Include PopPK data, e.g. covariate analysis, if available.

If there are differences in PK between healthy subjects and patients, this should be explained.

Depending on the amount of information, different sub-headings can be included.

If pharmacokinetics has mainly been documented in the target population and not in healthy volunteers, this section can simply cross-refer.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  If a modelled approach is used to inform the PK in a special group, assess the robustness of the data to support a high regulatory impact claim such as a contra-indication, dose adjustment or precaution of use.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Therapeutic window

Based on the data from clinical trials, describe the no‑effect boundaries which represent the interval within which a change in systemic exposure measure is considered not significant enough to warrant clinical action. In the following sections, the PK results of studies in special populations such as hepatic impairment and renal impairment or drug-drug interaction studies should be interpreted based on the no-effect boundaries.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Special populations

This section is not relevant for biosimilars.

In the sections below, provide the available PK of parent drug and active metabolites in special populations. Please add additional sections if relevant.

Please populate these sections with data from CTD module 5.3.3.3, Intrinsic factor PK study reports and CTD module 5.3.3.5 PopPK study reports (the presentation of data should be similar to preceding sections and should be included in Table 1, above).

Exploratory analysis of data across studies that may contribute to the understanding of variations in drug PK and possible statements on the consequences may be displayed here. These variations may be related to extrinsic or intrinsic factors such as age, weight, gender, ethnic factors, pregnancy/lactation, renal function and hepatic insufficiency. Results of PopPK covariate analyses should be presented.

Specific results for special populations should be presented in the appropriate sections below (2.2.8.1. to 2.2.8.7.).

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  The section above should only include a presentation of data across studies to inform on the PK variations seen in special populations vis‑a‑vis the target population. Only comment on these variabilities and whether they would have any clinical consequences and should be adequately described in the SmPC.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Impaired renal function

Please include references to Table 1 above (a dedicated renal impairment study should be presented in the table at the start of section 2.).

Intrinsic factor PK study reports. Generally, data should be evaluated using absolute GFR (ml/min) and not body size-adjusted GFR (ml/min/1.73 m2). For highly protein bound drugs data on unbound exposure should be presented. In addition, the applicant may include a statement on whether the entire eGFR range has been included and whether a relationship between renal function and exposure was detected or not.

In the event that no dedicated study has been performed this should be shortly justified; data (from literature or PopPK covariate analysis) should be given substantiating the relationship between renal function and exposure.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Is a dedicated study on renal impairment available? If so, the method for grading subjects with renal impairment should be assessed with regard to the recommendations of use in this sub-group of patients in the proposed SmPC.  If no such study is available, is the lack of data adequately reflected in the SmPC?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Impaired hepatic function

Please include references to Table 1 at the beginning of section 2. In the event a dedicated hepatic impairment study has been conducted; please state the degrees of hepatic impairment included, state the relationship between hepatic impairment and exposure.

For highly protein bound drugs, data on unbound exposure should be presented.

In the event that no dedicated hepatic impairment study is conducted: justify the absence of a dedicated study and provide (literature) data substantiating the relationship between degree of hepatic impairment and exposure.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Is a dedicated study on hepatic impairment available? If so, the method for grading subjects with hepatic impairment should be assessed with regard to the recommendations of use in this sub-group of patients in the proposed SmPC.  If no such study is available, is the lack of data adequately reflected in the SmPC?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Gender

Please provide a short statement on whether gender differences were investigated as a covariate on drug PK and whether it was found to be of significance.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  If any gender differences have been noted, assess whether these are appropriately reflected in the SmPC.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Ethnic factors

Please provide any data that outline potential differences in PK based on ethnic factors. Include a discussion regarding the numbers of subjects/patients of each ethnicity and if these are sufficient to draw appropriate conclusions.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  If any differences based on ethnicity have been noted, assess whether these are appropriately reflected in the SmPC.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Weight

Please provide any data that outline potential differences in PK based on body weight. State the weight range of the studied population. Particular focus should be made on availability of data on obese and under weighed subjects.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  If any differences based on weight have been noted, assess whether these are appropriately reflected in the SmPC.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Elderly

Table 2: Age ranges studied in the elderly population

|  | Age 65-74 (Older subjects number /total number) | Age 75-84 (Older subjects number /total number) | Age 85+ (Older subjects number /total number) |
| --- | --- | --- | --- |
| PK Trials |  |  |  |

This table will be relevant for the majority of medicinal products. Please consider that specific PK studies in older subjects should be presented or the absence of such studies should be acknowledged.

If PK in older people is likely to be altered, e.g. due to renal impairment, the need for dose adjustment should be discussed.

Statements made after consideration of these data should be meaningfully reflected in the product information.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:   1. If any differences in the elderly population have been noted, assess whether these are appropriately reflected in the SmPC.   <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Paediatric population

If the claimed indication includes paediatric patients, please follow the guidance below. If the claimed indication does not include paediatric patients, very briefly mention whether a PIP or PIP waiver has been agreed and what paediatric subsets (if any) will be investigated.

Please refer to the published guidelines on the use of extrapolation ([structured-guidance-use-extrapolation\_.pdf (europa.eu)](https://www.ema.europa.eu/en/documents/scientific-guideline/structured-guidance-use-extrapolation_.pdf)) and the reflection paper on the use of extrapolation to paediatrics ([Reflection paper on the use of extrapolation in the development of medicines for paediatrics - Final (europa.eu)](https://www.ema.europa.eu/en/documents/scientific-guideline/adopted-reflection-paper-use-extrapolation-development-medicines-paediatrics-revision-1_en.pdf)). Provide a summary of the extrapolation concept.

Further guidance on how to present data in support of a paediatric dose could be found here <https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-pharmacology-pharmacokinetics/modelling-simulation-questions-answers>

State whether studies in paediatric subjects have been conducted or not. Provide a brief reference to the PIP (e.g. as to whether future PK studies are planned). In case extrapolation is used to support a paediatric indication, available data on exposure supporting the indication should be reported here, with a cross reference to section 2.1.3.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:   1. If a paediatric indication is claimed, assess the uncertainties of the extrapolation and whether use in the paediatric population is appropriately reflected in the SmPC.   <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Pharmacokinetic interactions studies
       1. In vitro

Please state for which transporters and enzymes the active substance is a substrate with a cross-reference to the section where the data has been presented.

Please present here all in vitro experiments to address interaction risks.

Please complete the tables below based on data from CTD module 5.3.2 in vitro studies. The tables can be adjusted as needed, but please do not paste eCTD tables as figures (the text must be editable). When relevant, the inhibition parameters should be compensated for non-specific binding or degradation.

Table 3: Cut-offs for the evaluation of interaction potential

|  |  |  |  |
| --- | --- | --- | --- |
|  | 50×Cmax(u)a  (µM) | 25×Inlet Cmax(u)a  (µM) | 0.1×dose/250 mlb  (µM) |
| Parent drug |  |  |  |
| Metabolite 1 |  | NA | NA |
| Metabolite 2 |  | NA | NA |

a Multiple dose Cmax, xxx mg dose (study YYY)

b Based on a xxx mg dose

NA - Not applicable

<Text>

Table 4: Summary of in vitro enzyme inhibition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Enzyme | Substrate | Competitive inhibition | TDI | | Positive signal to evaluate further |
|  |  | Ki\* (μM) | KI (μM) | Kinact (min-1) | Yes/No |
| CYP1A2 |  |  |  |  |  |
| CYP2B6 |  |  |  |  |  |
| CYP2C8 |  |  |  |  |  |
| CYP2C9 |  |  |  |  |  |
| CYP2C19 |  |  |  |  |  |
| CYP2D6 |  |  |  |  |  |
| CYP3A4 |  |  |  |  |  |

<Text>

Table 5: Summary of in vitro enzyme induction

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Fold induction mRNA | | | | | | | | |
|  | CYP1A2 | | | CYP2B6 | | | CYP3A4 | | |
|  | Lot A | Lot B | Lot C | Lot A | Lot B | Lot C | Lot A | Lot B | Lot C |
| Concentration 1 |  |  |  |  |  |  |  |  |  |
| Concentration 2 |  |  |  |  |  |  |  |  |  |
| Concentration 3 |  |  |  |  |  |  |  |  |  |
| Concentration 4 |  |  |  |  |  |  |  |  |  |
| Concentration 5 |  |  |  |  |  |  |  |  |  |
| Positive control |  |  |  |  |  |  |  |  |  |

If induction of other enzymes has been studied add information in a separate table.

<Text>

Table 6: In vitro transporter inhibition

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Transporter | Substrate | In vitro system | Ki\* (μM) | Positive signal (Y/N) |
| P-gp |  |  |  |  |
| BCRP |  |  |  |  |
| OATP1B1 |  |  |  |  |
| OATP1B3 |  |  |  |  |
| OAT1 |  |  |  |  |
| OAT3 |  |  |  |  |
| OCT2 |  |  |  |  |
| OCT1 |  |  |  |  |
| MATE1 |  |  |  |  |
| MATE2 |  |  |  |  |
| BSEP |  |  |  |  |

\* If IC50 is used instead of Ki a justification should be provided (including linearity, choice of substrate concentration etc.)

Only include additional text if considered necessary to explain the data in the tables above e.g. further evaluation of positive signals such as results from the mechanistic static model. Please keep it concise.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Discuss study designs including concentration ranges, positive controls and stability of the test compound. Discuss in vivo relevance of observed inhibition. If the applicant has presented IC50 and not Ki data, assess justification and consider if e.g. use of IC50/2 as an estimate for Ki is appropriate. If the RIS model or mechanistic static model is used, the qualification of the system should be presented and its validity for the specific study be assessed along with the study results.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. In Silico

Please populate with data from various eCTD modules depending on the question being answered.

Please discuss the role of PBPK models. How do simulated data compare to the in vivo data? Discuss confidence in in–silico predictions based on submitted or literature data and the impact on dosing recommendations. Is the in house or commercial PBPK platform qualified for the intended purpose?

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. In vivo

Briefly describe performed clinical interaction studies. Please fill in the table including summary of clinical DDI studies (to be completed by applicant).

Table 7: Summary of clinical DDI studies

|  |  |  |  |
| --- | --- | --- | --- |
| Comparison | Substance Ratio, as Percent (90% CI) | | Dosing Recommendation |
| Cmax | AUCinf |  |
| Victim | | | |
| Effect of co-administration with X | 130 (100, 160) | 130 (117, 135) | No adjustment |
| Effect of co-administration with Y | 190 (150, 390) | 250 (380, 600) | Reduce dose by half |
| Perpetrator | | | |
| Effect on substance X |  |  |  |
| Effect on substance Y |  |  |  |

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Comment on the study design and mechanistic prediction of other interacting drugs based on the results. Conclude if “positive” results in in vitro inhibition/induction studies have been followed up in vivo with appropriate probe substrates. Discuss if the interaction potential may be different in certain subgroups intended for treatment (e.g. poor metabolisers, patients with RI etc).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Exposure relevant for safety evaluation

Summarise the exposure expected in the target population at steady state. Describe whether there is any specific sub-population with increased or reduced exposure and what the consequences are expected to be. To be used in non-clinical safety evaluation of exposure margins.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Does the exposure in the target population support the proposed posology? Does the SmPC advise regarding any posology modifications in populations with reduced or increased exposure?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Pharmacodynamics
     1. Mechanism of action

Please describe the mode of pharmacodynamic action in relation to the clinically desired primary pharmacological (therapeutic) effects (primary pharmacodynamic action). The choice of the PD biomarkers should be justified in relation to the mechanism of action in this section and the discussion of the clinical relevance should be specified below (section 2.3.2.).

In addition, taking into consideration the nature of the substance(s) under investigation, potential secondary pharmacodynamic actions should be described.

If available, briefly describe mechanistic modelling non-clinical work to characterise the mechanism of action. Please refer to the non‑clinical assessment report for more detailed information.

Please describe if clinical PK/PD models provide further insight on the proposed mechanism of action. Consistency shown in the clinic with the non-clinically identified mechanism of action and mechanistic modelling should be described.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Assess the validity of the human models and their relevance with regard to the therapeutic effects. Are the biomarkers used relevant? Has the mechanism of action been sufficiently characterised? And is the description in the SmPC adequate?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Primary pharmacology

This section should include studies on the mode of action and/or effects of the drug in relation to its desired therapeutic target. The design of the studies, including PD endpoints should be critically commented on in terms of clinical relevance of biomarkers, range of doses tested and number of individuals/time of PK and PD samples included. These studies are conducted at an early stage of clinical development to elucidate the mechanism of action, provide preliminary proof of concept (PoC) and to characterise the range of exposures or doses that are likely or not to have a therapeutic effect in patients and to be further investigated in dose ranging efficacy and safety trials.

In addition, these studies should investigate covariate effects on primary pharmacology i.e. effects of age or genetic polymorphism on PD (or PK/PD) relationships. It is acknowledged that the extent of population exposure in early phase of development may be limited and that further covariate analyses should be conducted in later stages of development, even post marketing.

Results from special studies (e.g. immunogenicity and microbiology) could be described here.

Early dose finding studies are particularly important to describe, although the main dose-finding studies (section 3.2.) should not be repeated here.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Any modelling and simulation approaches used to link dose, exposure and PD, including covariate effects should be assessed. In particular, is there consistency of assumptions on primary pharmacology across non-clinical development and throughout clinical development?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Secondary pharmacology

Describe the secondary pharmacology (as related to the indication). Please include general features of tolerability in healthy volunteers with regard to secondary pharmacology on relevant dynamic endpoint studies, e.g. 24- hour blood pressure, biochemistry, virus levels, ECG, EEG etc.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it has any influence on the proposed indication/posology or any other sections in the SmPC.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Pharmacodynamic interactions with other medicinal products or substances

Please describe interactions of interest with other medicines and any kind of substances with an impact on the dosing recommendations. The proposed text for the SmPC with precautions or warnings should be also mentioned here.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Have potential interactions with other medicines been sufficiently characterised? Are the proposed recommendations in the SmPC adequate?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Genetic differences in PD response

Please describe any genetic difference in PD response as well as potential differences in the paediatric population (e.g. due to maturation).

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it influences the proposed indication/posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. <Immunological events>

If not relevant (e.g. vaccines), this section can be deleted.

Please mention antibody formation with regard to safety (e.g. neutralising antibodies, auto-antibodies, species-specific antibodies, such as HAMA (human anti-mouse antibodies) or HAHA (human anti-human antibodies) in the case of monoclonal antibody products). Discuss the validity/usefulness of the assay. Modelling and simulation may be helpful in understanding the PK profile of antibodies, PK/PD and the impact on safety or efficacy.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it influences the proposed labelling.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Pharmacokinetics-Pharmacodynamics (PK/PD)
     1. Relationship between plasma concentration and effect and safety

Briefly summarise data from CTD module 5.3.4 on PK/PD in healthy volunteers and patients.

If available, drug-exposure-response and PK/PD approaches based on data across studies should be described here. Please indicate if these analyses were used to define the time course of drug effects, the range of doses tested in early clinical development and if the selection of dose(s) and study duration for phase III was supported by these analyses. In addition, the covariate effects on PK/PD and drug-exposure-response relationships can be presented to identify clinical scenarios when the benefit-risk profile of the medicine may be altered resulting in the need for specific risk minimisation measures.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed indication/posology.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. Evaluation and Qualification of PK/PD Models

Please describe the development of the PK/PD model, exposure-response model and simulation methods together with all covariate analyses (hepatic, renal impairment the degree of the severity, gender, ethnic factors, prior use of medications) taken into account. PK/PD analyses in healthy subjects as well patients should be outlined. Any effects on potential biomarkers and/or disease progression should be mentioned.

Please state the rationale for the choice of the PK/PD model.

Different types of PK/PD models can be summarised in this section, e.g. from population PK/PD-based approaches to quantitative systems pharmacology (QSP) PK/PD models and mechanistic disease models.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:   1. Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it influences the proposed indication/posology.   <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Dose justification

Provide a summary of how PK/PD influenced the doses selected throughout the development programme, including, but not limited to, covariate analyses, exposure-response analyses, and simulations to justify the proposed posology.

Reference to model-independent (allometric scaling) or model-based (PK and physiologically based PK) approaches based on non-clinical data to determine the appropriate dose in humans, could be made, if relevant.

Please do not duplicate information included later in section 3.2. ; this section should focus on the PK/PD drivers for dose selection.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Assess if the applicant had a reasonable justification for the proposed posology (as included in section 4.2 of the SmPC) or if there is some uncertainty regarding the selected dose.  Has the proposed posology been sufficiently justified? Including adjustments for specific populations and coadministration of other medicines?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Overall Rapporteur assessment of Clinical Pharmacology
     1. Discussion

The contents of this section should be written so that they can be copied/pasted directly into the CHMP AR/Overview.

One could consider a specific heading relating to the pharmacology and microbiology when the medicinal product under evaluation is anti‑infective.

Have the pharmacokinetics of parent drug and active metabolites been sufficiently documented in special populations?

Has adequate information regarding pharmacokinetics in special populations and possible lack of information been included in the SmPC (restrictions/precautions/dose adjustments)?

Have PopPK analyses been conducted and have all important covariates been explored to explain interindividual or intra-individual variability in PK? Do exposure-response or PK/PD analyses together with clinical data suggest that unexplained or explained variability in PK may change the benefit-risk profile of the medicine in certain clinical scenarios and thus specific risk minimisation measures should be included in the RMP such as restrictions/precautions/dose adjustments in special populations or therapeutic drug monitoring or a post-authorisation safety or efficacy study.

Comments regarding performed interaction studies.

Have appropriate conclusions been drawn from the performed in vivo studies?

Do PBPK modelling or PopPK modelling support in vivo data? Do PBPK and PopPK suggest additional PK interactions?

Are there any other potential clinically relevant interactions e.g. inhibition or induction of enzymes/transporters that have not been studied? Are additional in vitro, in vivo or in silico drug interaction studies needed and can these be done post-authorisation?

Do exposure-response or PK/PD analyses together with clinical data demonstrate that PK interactions may change the benefit-risk profile of the medicine in certain clinical scenarios and thus specific risk minimisation measures should be included in the RMP such as restrictions/precautions/dose adjustments or therapeutic drug monitoring?

For further guidance, please consult the [Guideline on the investigation of Drug Interactions](http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129606.pdf).

Discuss conclusions relating to bioequivalence or dosage adjustment in the SmPC if necessary.

Consider whether efficacy might be reduced in the older adult population due to PD changes.

Lack of information in certain groups of patients (renal/hepatic impairment, children, elderly, women with childbearing potential etc.) should be mentioned to qualify statement made in section 4.4 of the SmPC and it should be mentioned here.

PK interaction studies: Comments on interactions with other medicinal products, interaction with food (if not addressed under absorption or pharmacodynamic interaction above) and dynamic interactions should be provided if data are available. Separate clearly pharmacokinetic from pharmacodynamic interactions. Possible interactions with herbal remedies and the possible clinical implications.

Dose response studies: Assess justification for surrogate endpoints and results outlining how these studies have contributed to confirmation of efficacy, e.g. acute diseases such as infectious diseases and pain may rely on fixed-dose studies in which case the points outlined under the next heading (“Main studies”) should be considered.

For biosimilars: The above is not applicable. Discuss the adequacy of methods (assays) and trial design used for analysis with particular attention to selection of dose and protein correction, if applicable. Discuss the results of the PK and/or PD comparability study(ies) obtained against the chosen reference medicinal product also taking into consideration prior pharmacologic knowledge of the product. Discuss the sensitivity of the endpoints and model used to detect potential product-related differences as well as the margins chosen for the comparison. When applicable, discuss any potential impact of anti-drug antibodies on PK data. Discuss the PK and/or PD bridging data (e.g. when several routes of administration are proposed, when a non-EU comparator is used in some (non)clinical studies), if applicable.

Discuss the claimed mechanism of action and the PD data supporting the mechanism of action (both primary and secondary effects) and describe the uncertainties and the relevance of uncertainties.

Discuss pharmacodynamic interactions and the potential label thereof in the SmPC.

Discuss the exposure-response data, especially with respect to an adequate dose selection for phase III.

Highlight areas of disagreement and any issues requiring clarification. Include comments on the suitability of the proposed SmPC text.

<Text>

* + 1. Product information

Comments and edits can be made directly in the annexes (product information) and do not need to be repeated here. Use this section for a more general assessment of the adequacy of the proposed SmPC.

<Text>

* + 1. Conclusions

A very brief summary of the conclusions drawn from the clinical pharmacology documentation should be provided here.

For biosimilars, conclude if the available PK/PD data support biosimilarity versus the EU reference product. In addition, if a non-EU comparator has been used, conclude whether it is representative of the EU reference medicinal product.

Any questions not already included in the sections above can be added here and later transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.

<Text>

1. Clinical efficacy

Please complete section 3 of this report based on eCTD sections 2.5, 2.7.3. and 5.3.5. Include also completion of template tables as reported below. Use of additional tables for reporting of data is also encouraged in any of the subheadings. Avoid repetition of the same data between text and tables.

Simple copy/paste from the dossier modules 2.5 and 2.7.3 is not acceptable, a degree of simplification is expected. Hence, decide on the minimum detail on individual studies (aim: balanced presentation of “positive” and “negative” findings). Please also include a cross reference to the relevant section of the eCTD.

Distinguish between pivotal trials and supportive trials based on judgement on individual importance (mention all studies, if possible, referring to tabulated summaries).

In each relevant section below, summarise clearly which data are reflected in the proposed SmPC, which are not, and why.

* 1. Clinical development

Please complete the following tabular overview of the relevant clinical studies. Such a table should be aligned with the CTD table 2.7.3.1 (although fewer columns are required).

Table 8: Clinical studies

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Study ID | Enrolment status  Start date  Total enrolment/ enrolment goal | Design  Control type | Study & control drugs  Dose, route of administration and duration  Regimen | Population  Main inclusion/ exclusion criteria |
| <text> |  |  |  |  |
|  |  |  |  |  |
|  |  |  |  |  |

Only use the text section below if an explanation is needed for the table above.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Briefly describe whether the development plan in principle supports the proposed indication.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Dose response study(ies)

Please briefly describe study designs and methods of studies contributing to selection of one or more doses used in the main (pivotal) studies. Please consider size, number and range of studied doses and justification of endpoints.

Please discuss results and outline how these contributed to the objectives of dose and dosing schedule selection, characterisation of exposure/response relationship and Proof of Concept. However, please avoid repetition of section 2.2. and use cross-references where possible.

In case dose response studies are lacking, please provide a justification for the choice of dose in this section.

If the pivotal trial has a dose-escalation phase, please mentioned it briefly here and include it in section 3.3. with the overall study design.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Have sufficient exposure/response studies and/or modelling been carried out to support the proposed posology?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Main study(ies)

The Applicant should complete the sections below for each pivotal study presented.

Note: In the case of multiple pivotal phase 3 studies with similar methodologies a summary of the common methodology is preferred. Individual features of each study may then be described under the heading of each individual study. As for the Methods, Results can be reported jointly or separately for each trial (depending on the degree of similarity in study designs and outcomes). Justification for combining results should be provided together with the implication for the interpretation of the data.

* + 1. <Study #1 identifier> <Study title>

{Repeat this whole section (3.3.1 and its subheadings) for each pivotal study}

Table 9: Study identifiers

|  |  |
| --- | --- |
| Study code |  |
| EU CT number |  |
| NCT number |  |
| ISRCT number |  |
| Other identifier(s) |  |
| Location in eCTD |  |

* + - 1. Study design

Describe the main design elements of the study; phase, randomisation, open‑label or blinded, comparator, number of study arms, duration of treatment, etc. This section should be in line with [ICH M11 template, section 6](https://www.ema.europa.eu/en/documents/scientific-guideline/ich-m11-template-step-2b_en.pdf).

<Text>

Figure 3: Study schema

Insert a schematic representation of the study design.

<Figure>

* + - * 1. Study population

Describe the study population, the geographical locations in which the study was conducted and the main inclusion/exclusion criteria. If a companion diagnostic was used to screen participants at entry, describe it here.

<Text>

* + - * 1. Randomisation and blinding

If applicable, describe the method used for randomisation and blinding. Also describe the criteria for emergency unblinding.

<Not applicable><Text>

* + - * 1. Description of trial intervention

Describe the intervention to be administered in each arm of the trial and for each period of the trial including route and mode of administration, dose, dosage regimen, duration of intervention. Include information for all trial interventions (experimental, placebo, active comparator, sham comparator).

Indicate whether an additional product was to be provided as part of the trial and its intended use (background intervention, challenge agent, diagnostic, or other). Include dosing information.

<Text>

* + - * 1. Concomitant and rescue therapies

If relevant, describe any permitted or prohibited concomitant medications and the reasons for allowing/prohibiting. Also if relevant, describe any rescue therapies that could be used during the course of the trial.

<Not applicable><Text>

* + - * 1. Study assessments

Describe the methods used for the assessment of efficacy (e.g. blood test, CT scan, MRI, biopsy, functional measurements, Patient reported outcomes, etc...). Describe if their use is consistent across treatment arms (e.g. in relation to the timing of the assessments) and if it is consistent with treatment and/or diagnosis guidelines and clinical practice. If relevant, include a description of the schedule of activities/assessments and, if applicable, provide description of planned or unplanned changes in the conduct of the study.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided. Does the planned study (population, choice of randomisation/comparator, duration of treatment, etc) adequately address the indication/posology claimed in the SmPC? Do any planned/unplanned changes in the study conduct impact the interpretation of the results?  Are the planned study efficacy assessments sufficient for the intended purpose? Are the methods clinically validated? Are the assessments performed equally between treatment arms and, if not, is this justified?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Objectives, endpoints and estimands
         1. Primary Objective

Present the specific objective and hypothesis. State the statistical hypothesis (e.g. superiority, equivalence or non-inferiority). In case of non-inferiority or equivalence, please describe the (pre-defined) non‑inferiority or equivalence margin(s) with justifications.

<Text>

* + - * 1. Estimand<s> for the primary objective

Table 10: Estimands for primary objective

|  |  |
| --- | --- |
| Population | Choose those that apply and delete the rest  <Patients with [condition and applicable specifiers] who would encounter the Intercurrent Event of [intercurrent event] if assigned to [treatmentName].>  <Patients with [condition and applicable specifiers] who would not encounter the Intercurrent Event of [intercurrent event] <if assigned to [treatmentName].>  <Patients with [condition and applicable specifiers] who would encounter the Intercurrent Event of [intercurrent event] under any treatment assignment.>  <Patients with [condition and applicable specifiers] who would not encounter the Intercurrent Event of [intercurrent event] under any treatment assignment.> |
| Treatment condition<s> | Choose the statement that applies (modifications allowed) and delete the rest  <Assignment to [treatmentName], regardless of discontinuation, compared to assignment to [comparatorName], regardless of discontinuation.>  <Assignment to [treatmentName] and [additional medication] as needed, regardless of discontinuation and use of additional medications, compared to assignment to [comparatorName] and [additional medication] as needed, regardless of discontinuation and use of additional medications.>  <Assignment to [treatmentName], regardless of discontinuation and added to [background medication] compared to assignment to [comparatorName], regardless of discontinuation, added to [background medication].>  <Assignment to [treatmentName] in the hypothetical scenario of no discontinuation compared to assignment to [comparatorName] in the hypothetical scenario of no discontinuation.>  <Assignment to [treatmentName] and [additional medication] as needed, in the hypothetical scenario of no discontinuation compared to assignment to [comparatorName] in the hypothetical scenario of no discontinuation and use of additional medications.>  <Assignment to [treatmentName] and [additional medication] as needed, in the hypothetical scenario of no discontinuation, added to [background medication], compared to assignment to [comparatorName], regardless of discontinuation, added to [background medication].> |
| Endpoint (variable) | [name of the variable or outcome to be observed from every participant] at [timepoint] <or before the occurrent of the [intercurrent event]> |
| Population-level summary | [Population-level summary, e.g. difference in means] |
| Intercurrent events and strategy to handle them | |
| <Intercurrent event 1> | <Treatment policy> <Hypothetical> <Composite> <While-on-treatment> <Principal Stratum> |
| <Intercurrent event n> | <Treatment policy> <Hypothetical> <Composite> <While-on-treatment> <Principal Stratum> |

Describe the clinical question of interest (i.e. a **short** description of the estimand(s) in plain language), followed by intercurrent events and the strategies applied. The description should be based on the table above and not be too lengthy. If applicable, please substantiate the use of a surrogate endpoint.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Is the statistical hypothesis duly justified? Are the primary outcome measures clearly defined? Are the estimands justified? Is the strategy for intercurrent events also justified?  Assess the justifications provided by the applicant to support the validity of any surrogate endpoints, if applicable.  Briefly comment on the clinical relevance of the aforementioned endpoint(s).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - * 1. <Secondary> <Tertiary> objective

Specific objective and hypothesis. State the statistical hypothesis (e.g. superiority, equivalence or non-inferiority).

<Text>

* + - * 1. Estimand<s> for the <secondary> <tertiary> objective

Describe the clinical question of interest (i.e. a **short** description of the estimand(s) in plain language), the intercurrent events and strategies applied, followed by the specific attributes in the table above. It is advised to include a table for at least the key secondary estimand(s); in such case copy and paste in this section Table 10 above used for primary objective estimands, including the text and the commenting boxes. The table could also refer to another estimand table to avoid duplications of text. If applicable, please substantiate the use of surrogate endpoints.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Are the secondary and tertiary (if relevant) outcome measures clearly defined?  If appropriate, focus on the most important secondary endpoints. Assess the justifications provided by the applicant to support the validity of any surrogate endpoints, if applicable.  Discuss the validity of any surrogate endpoints.  Brief comments on the clinical relevance of the aforementioned endpoint(s).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Statistical methods for estimation and sensitivity analysis
         1. Planned analyses

The description should start with a concise description of analysis sets, followed by the main analysis methods for primary and important secondary endpoints. Statistical tests and estimation methods should be described with all relevant details. The description should refer to estimands defined above where applicable. Include a description of the applied methods for multiplicity control whenever necessary (e.g. across endpoints or interim analyses). Handling of missing data should be briefly described, then briefly sensitivity or supplementary analysis method(s).

<Text>

* + - * 1. Planned subgroup analyses

Describe the planned subgroup analyses.

<Text>

* + - * 1. Sample size determination

Describe the method used for the sample size calculation.

<Text>

* + - * 1. Error probabilities, adjustment for multiplicity and interim analyses

Describe the error probabilities, adjustment for multiplicity and interim analyses.

<Text>

* + - * 1. Changes from protocol-specified analyses

Describe any changes made to the Statistical Analysis Plan and /or any ad hoc or unplanned analysis.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Is the Statistical Analysis Plan adequate to support the testing of the hypothesis? Are the power and sample size calculations adequate? Comment on the validity of the analysis planned and the validity of any changes to the SAP (planned or post hoc).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Data quality assurance

Very briefly describe the quality assurance step in place during and after the conduct of the study, e.g. training, monitoring, data collection and analyses, and audits.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Comment on whether the data quality assurance measures put in place are considered adequate. If any areas of concern, comment on the potential need for an inspection. Note, there is a dedicated section later in the document for GCP aspects (section 3.8.).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - 1. Results
         1. Changes in the planned conduct of the study

Describe any substantial protocol amendments implemented during the conduct of the study. The changes should be well described and justified. Please include the dates at which relevant changes were introduced in context of the trial conduct (e.g. changes prior to recruitment start, changes prior to/after interim analyses/database lock/unblinding).

Changes to the Statistical Analysis Plan should be described in section 3.3.1.3.5. below and not here.

Please provide information on protocol compliance and GCP inspection findings, if applicable.

<Text>

* + - * 1. Participant flow and numbers analysed

Please include dates defining the periods of recruitment and follow-up. The start and the end of trial dates would be useful.

Please describe the flow of the progress of study participants through all the phases of the trial (Please use the diagram as suggested below with minimal textual explanation).

Specifically, for each group, please report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analysed for the primary outcome, e.g.:

* Enrolment (No. subjects screened; No. randomised; No. excluded and reason, dates defining the periods of recruitment).
* Allocation (by treatment arm, No. randomised, No. started allocated treatment, No. that did not start allocated treatment and reasons).
* Follow-up (by treatment arm, No. lost to follow-up and reasons; No. protocol treatment discontinuation; dates defining the periods of follow-up). Median follow-up at data cut-off data should be presented.
* Treatment discontinuation numbers and study discontinuation numbers should be clearly distinguished.
* Analysis (No. included into set for analysis of primary estimation; No. excluded and reasons).

Describe the most common reasons for screen failures.

Describe criteria for rescue treatment and for early escape if relevant for the understanding of the interpretation of the results.

Please provide the number of participants (denominator) in each group included in each analysis dataset and whether the analysis was by “intention to treat”. State results in absolute numbers (e.g., 10/20 not 50%). Please provide the number of patients recruited, withdrawn, discontinued (from treatment or study) for any reason. Numbers of patients having an intercurrent event (as described in section 3.3.1.2.2. Estimand<s> for the primary objective) should be provided according to each particular intercurrent event. Be clear which instances result in missing data. Specify how patients and data points were included in or excluded from the analysis with a justification based on the selected strategy and estimator.

<Text>

Figure 4: Participant flow

Randomized (n= )

Assessed for eligibility (n= )

Excluded (n= )

♦  Not meeting inclusion criteria (n= )

♦  Declined to participate (n= )

♦  Other reasons (n= )

Analysed (n= )  
♦ Excluded from analysis (give reasons) (n= )

Lost to follow-up (give reasons) (n= )

Discontinued intervention (give reasons) (n= )

Allocated to intervention (n= )

♦ Received allocated intervention (n= )

♦ Did not receive allocated intervention (give reasons) (n= )

Lost to follow-up (give reasons) (n= )

Discontinued intervention (give reasons) (n= )

Allocated to intervention (n= )

♦ Received allocated intervention (n= )

♦ Did not receive allocated intervention (give reasons) (n= )

Analysed (n= )  
♦ Excluded from analysis (give reasons) (n= )

## Allocation

## Analysis

## Follow-Up

## Enrollment

|  |
| --- |
| (Co)-Rapporteur’s comments:  Comment on the participant flow. Whether any of the reasons for screen failure or discontinuation from treatment or study could have an impact on the validity of the results.  Discuss treatment compliance, if appropriate.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - * 1. Baseline data

Please describe demographic and clinical characteristics of each group.

Please describe particularly any asymmetry in characteristics across treatment arms. A table format for data presentation is preferred. For examples of table formats, see Annex I. Please include a reference to the relevant eCTD section under each data table.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Discuss if the study population reflects the intended indication.  Discuss similarities and any discrepancies between treatment arms (if applicable).  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - * 1. Outcomes and estimation

Please describe outcomes and estimations starting with the primary objective, the estimand and the endpoint. Minimize the use of text and rather use Kaplan-Meier curves and Forest Plots (where applicable), or data tables. Please include a reference to the relevant eCTD section under each data table.

If critical to the interpretation of the study, include brief data tables (or plots) for important secondary endpoints that provide additional information. Secondary endpoints that are highly correlated to the primary endpoint, tertiary and exploratory endpoints need not be discussed. Provide a summary of results with estimated precision (e.g. 95% CI).

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Does the data provided demonstrate an effect for the product at the proposed dose in the target population? If not, what additional data is needed to determine an effect?  Discuss the clinical relevance of the observed effects and whether they support the proposed indication.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - * 1. Pre-defined and ad hoc important subgroup analyses

Please describe outcomes and estimations of all pre-defined subgroup analyses and ad hoc important subgroup analyses. Minimize the use of text and rather use Kaplan-Meier curves and Forest Plots (where applicable), or data tables. Please include a reference to the relevant eCTD section under each data table.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Does the data provided demonstrate an effect for the product at the proposed dose in the target population? If not, what additional data is needed to determine an effect?  Discuss the clinical relevance of the observed effects and whether they support the proposed indication.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + - * 1. Ancillary analyses

This section should only be used in cases where additional analysis not described above were performed. Subgroup analyses should be presented in the main outcomes section (section 3.3.1.5.4.) not here.

Examples that could be included here are post-hoc analyses, adjusted analyses, including pre-specified ones and other post hoc techniques.

Modelling and Simulation (M&S) analyses (e.g. PopPK, PopPK/PD) may support use in a target population different from the study population. In this event, a reference to section 2.2 in combination with a short statement on which group of patients should be additionally covered may be included.

<Not applicable><Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Are any of the analyses above sufficiently justified? Can these analyses support the claims in the SmPC?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* + 1. <Study #2 identifier>

In case of multiple pivotal studies, please copy paste in this section the whole of the headers for section 3.3.1. and subsequent subheadings above, including the tables and the commenting boxes. Repeat this process as per the number of pivotal studies submitted in the dossier.

If only 1 pivotal study, delete this heading.

<Text>

* 1. Subgroup analyses/clinical studies in special populations

This section is not relevant for biosimilars.

Please include in this section special studies e.g. in children, in the elderly, in pregnant or lactating women and in patients with renal or hepatic impairment. Please describe these studies as suggested for the main studies including considerations on dose adjustments. If a paediatric indication is sought, briefly refer to the PIP.

If the disease/condition is prevalent in a specific sub-population of subjects, any specific data in those subjects should be presented or the absence of such studies should be justified.

Statements made after consideration of these data should be meaningfully reflected in the product information.

Table 11: Clinical studies in special populations

|  | Controlled Trials | Non-controlled trials |
| --- | --- | --- |
| Renal impairment\* patients (Subjects number /total number) |  |  |
| Hepatic impairment\*\* patients (Subjects number /total number) |  |  |
| Paediatric patients <18 years (Subjects number /total number) |  |  |
| Age 65-74 (Subjects number /total number) |  |  |
| Age 75-84 (Subjects number /total number) |  |  |
| Age 85+ (Subjects number /total number) |  |  |
| Other (Subjects number /total number) |  |  |

\* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)

\*\* Hepatic impairment is defined as having Child-Pugh score B or C

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. In vitro biomarker test for patient selection for efficacy

If no biomarker test is used, please state “not applicable”.

If applicable, please provide the scientific rationale for the choice of the predictive in vitro biomarker test (e.g. prevalence, relation to disease mechanism).

Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out method.

Analytical and clinical validation strategy:

* Analytical validity: For verifying the suitability of an assay, robustness, accuracy, specificity, sensitivity and linearity should be considered depending on the analytical platform
* Clinical validity (sensitivity/specificity) should be described either by correlation with a clinical endpoint (for novel assays) or –if available- by concordance study with a clinically valid reference assay
* Cut-point selection should be described and discussed in detail since it is of particular importance for the benefit /risk assessment.

<Not applicable><Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Note, this is not the “assessment of suitability” of a companion diagnostic, as initiated by a Notified Body. Here you are simply asked to determine the scientific rationale whether the assay used was appropriate for patient selection and whether it was reasonable for that subset of the population to be chosen.  <Not applicable><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Analysis performed across trials (pooled analyses AND meta-analysis)

This section should only contain the combined analyses from several trials, as included in the Integrated Summary of Efficacy.

Please state the criteria (rationale and potential bias) used for these analyses and consider if these may involve exploratory analysis on the whole database considering different effect modifiers (gender, age, pregnancy, lactation, drug-disease interactions, smoking etc.).

As for previous sections, minimize the use of text and rather use Kaplan-Meier curves and Forest Plots (where applicable), or data tables. Please include a reference to the relevant eCTD section under each data table.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Supportive study(ies)

Please describe any relevant studies not already included in the sections above. These should be concisely addressed adopting a cumulative approach.

If any Real-World Data (RWD) is used in support of the SmPC claims, please describe the data sources used and their purpose.

If RWD is e.g. used to provide an external control arm it should be part of the corresponding pivotal study and should be reflected in the methods section of that assessment, not here.

This section should also ideally include brief results of the feasibility analyses performed by the applicant justifying why such data sources were used instead of others and explaining the suitability of those sources to answer the research question(s). If the use of RWD was agreed in scientific advice, this should be clearly stated. The concept of feasibility analysis is described in the [CHMP guideline on registry-based studies](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-registry-based-studies_en-0.pdf), also applicable to other data sources than registries.

<Nor applicable><Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  What is the relevance of such supportive studies? Their added value, as well as their possible limitations should be described (e.g. data representativeness, quality, missingness, risk of confounding and bias, lag time, suitability based on study design). Include a clear statement of whether the inclusion of such data and associated claims in the SmPC is accepted or rejected.  To support the assessment of the present application, the Rapporteur might request EMA to provide additional RWD, including from DARWIN EU. In this case, please provide a short summary of the research question and study request via email to RWE@ema.europa.eu.  In case EMA already provided RWD (e.g. from DARWIN) upon request from CHMP to support its evaluation, a description of the evidence and its impact on the assessment should be included.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. <Patient><and><healthcare provider> engagement>

Please delete this section if not relevant.

If there was patient and/or HCP engagement that had an impact on this product during clinical development, please summarise this very briefly. Examples include specific guidance from HCPs/patients on the importance of the use of endpoints, assessments, disease impact, PROs, etc. Avoid any promotional language.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  What is the relevance of such engagement? The added value, as well as the possible limitations should be assessed as well as the possible impact on any SmPC wording.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. GCP aspects

This section is to be filled by the Rapporteurs only.

Discuss the need for a triggered GCP inspection as part of the evaluation:

Of note a GCP inspection could be requested on a routine (surveillance) basis upon positive validation or on a triggered basis (based on the assessment).

Has a routine GCP inspection been already requested by CHMP?

Are there any concerns raised during the assessment about compliance with GCP and related regulatory and ethical requirements (data accuracy or protocol compliance and compliance with ethical aspects):

* Implausible results (e.g. biologically unlikely conflicting results between studies or sites)
* Critical dependence on a single or small group of studies
* Major impact factor - e.g. a vaccine to which an entire infant population might be exposed
* Novel therapy
* Potential for ethical concerns (vulnerable populations: paediatric, mentally impaired, lack of alternative therapy, institutionalised subjects, populations in developing world, etc
* Lack of inspection experience with geographical origin of data and/or data coming from developing countries
* Sponsor not previously inspected?

Detailed information on triggers for inspection can be found in the document “Points to consider for assessors, inspectors and EMA inspection coordinators on the identification of triggers for the selection of applications for “routine” and/or “for cause” inspections, their investigation and scope of such inspections” which is available in the EMA website [<http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/08/WC500148220.pdf>].

To request a triggered GCP inspection:

* Contact your local GCP inspectorate.
* Contact the PL and EMA inspection coordinator.
* Determine with them the clinical trial(s), sites and special concerns or issues to be addressed/the trigger or random factor related to the inspection.

All GCP inspections requests need to be reflected in the assessment report as follows:

For routine GCP inspections:

<A request for GCP inspection has been adopted for the following clinical study(ies) <enter study number(s)>. The outcome of this inspection and the satisfactory responses to its findings are an integral part of this procedure and will be needed by Day 181.>

For “for cause” i.e. triggered GCP inspections please describe the trigger(s) for inspection, as applicable, and add the following wording:

<A request for GCP inspection has been adopted for the following clinical study(ies) <enter study number(s)>. The outcome of this inspection and the satisfactory responses to its findings are part of the responses to the LoQ and will be needed by Day XXX.>

For GCP inspections/GCP compliance information received from other regulatory authorities please use the following wording:

<Additional information on GCP compliance of the studies included in this dossier were gathered from EU and non-EU regulatory authorities and were shared with the CHMP for consideration in the assessment as follows:

* a full inspection report/summary of inspection outcome of the GCP inspection by <enter name of EU authority > conducted at <enter type of site(s) i.e. investigator site> and <country of site inspected> in relation to study <enter study protocol number>;
* Establishment Inspection Reports from GCP inspection by Food and Drug Administrations (USA Regulatory Authority) of <enter information on sites inspected/type of site and country> for study <study number>.

<Text>

Based on the review of clinical data <and the above-mentioned reports>, CHMP <did not><did> identify the need for a <further> GCP inspection of the clinical trials included in this dossier.

* 1. Overall Rapporteur assessment of clinical efficacy
     1. Discussion

This section is to be filled by the (Co)Rapporteurs only, not the company.

The contents of this section should be written so that they can be copy/pasted directly to the CHMP AR/Overview.

The discussion is often the most important part of the assessment report. In terms of structure, it should in principle follow the flow of the presentation of results above.

Try to be as clear and concise as possible (often discussions are too long and verbose, and the true meaning of the data is not addressed).

For each section, the discussion should address the following points:

1. Identify the most important findings and deficiencies described above (do not repeat results). Describe how results agree. Summarise evidence for each conclusion.
2. Discuss if the data submitted fulfil the requirements (legal, guidelines, scientific advice)
3. Describe the major issues raised and how they were addressed
4. Highlight important issues expected for the CHMP discussion

Both study design and results should be subject to the critical discussion. Be explicit about the (Co)-Rapporteur’s view on key elements like choice of comparators, endpoints as well as shortcoming of the data. The following is a compilation of potential aspects to be addressed in such discussion.

Design and conduct of the clinical studies:

* Was the design of the studies adequate (randomised active and placebo-controlled trials)? If not, what are the justifications and are they acceptable?
* Was the patient population adequately selected (reflection on inclusion/exclusion criteria)?
* Is the comparator considered appropriate? In case of an active comparator, discuss the relevance in view of the EU approved treatment options.
* Critical discussion of the appropriateness of the choice of endpoints as well as the duration of the study considering regulatory guidance/scientific advice. Validity of surrogate markers to replace hard endpoints? Acceptability of a composite endpoint and its domains?
* Were the important estimands adequately defined and is it considered clinically relevant and acceptable?
* Were the analysis methods, appropriate and did they reflect the defined estimands.
* Is the design in accordance with legal requirements, available guidelines, scientific advice?
* Was the conduct of study adequate (also in the light of measures to blind patients and or the study team)? What impact could changes in the ongoing study have on the results?
* What are the implications of any GCP inspection?

For biosimilars, discuss the sensitivity of the endpoints and model used to detect differences as well as the margins chosen for the comparison.

Efficacy data and additional analyses:

* Precision of the effect estimate and support from secondary endpoints.
* What are the key findings (or uncertainties)? What key findings (or uncertainties) should be part of the benefit-risk assessment?
* Generalisability, internal and external validity of trial findings. Do the results support the (claimed) indication?
* Is the D-E-R (efficacy) relationship well characterised and the intrinsic extrinsic factors affecting this relationship well understood?
* Are any additional analyses/data required and what are the reasons for this request (e.g. longer term/follow up data)?
* If sub-group data is considered of particular relevance for the overall assessment of efficacy, this should be explained. Refer to the [Guideline on the investigation of subgroups in confirmatory clinical trials](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-investigation-subgroups-confirmatory-clinical-trials_en.pdf).
* Discuss any justifications for waiving certain studies or replacing original studies by literature data
* Is there lack of information in certain groups of patients (children, elderly women with childbearing potential etc.)? Should this have an impact on any of the sections of the SmPC?
* Which are specific considerations for the paediatric population, if any?
* How are the findings (or lack of information) reflected in the SmPC? Ensure correspondence with SmPC (particularly section 5.1) and that all information in the SmPC is explicitly assessed and supported by the scientific assessment.

Additional considerations:

- is there a need to convene a SAG?

- is there a need to trigger an inspection?

For biosimilars, discuss the results of the efficacy comparability study obtained against the chosen reference medicinal product, if applicable. Consider also available experience with the reference product for plausibility of results. Discuss if there are differences observed at quality (e.g. molecular structure, glycosylation profile, formulation), non-clinical level (e.g. target receptor binding, functional activity) or PK/PD level that could affect clinical efficacy. Discuss whether pre-existing or treatment-emergent anti-drug antibodies could have an impact on efficacy, also considering the relevance for potential extrapolation to other indications of the reference product.

<Text>

* + - 1. <Additional efficacy data needed in the context of a <conditional> MA <under exceptional circumstances>

Delete this section in the cases where there is no conditional MA or MA under exceptional circumstances.

The recommendation to grant a marketing authorisation under exceptional circumstances by the CHMP should carefully be considered for situations where, for a number of reasons, it does not seem possible to ever assemble a “full” dossier. Notably, a marketing authorisation under exceptional circumstances will normally remain under exceptional circumstances and not lead to a conversion into a normal marketing authorisation.

Describe here the missing data in Module 5, why it is missing (rarity of disease = exceptional, early development = conditional) and how the gap is foreseen to be bridged, i.e. which data is required to be submitted.

Any measure identified as a condition needs to be well motivated, notably the need for a condition should be explained in the context of a positive benefit/risk balance. In particular, conditions related to post-authorisation efficacy studies should explicitly refer to situation(s) as listed in the Commission Delegated Regulation (EC) No 357/2014.]

The following measures are necessary to address the missing efficacy data in the context of a <conditional> MA <under exceptional circumstances>:

<Text>

* + 1. Product information

Comments and edits can be made directly on the annexes (product information) and do not need to be repeated here. Use this section for a more general assessment of the adequacy of the proposed SmPC regarding efficacy.

Section 5.1 of the SmPC presents information relevant to the prescriber and other HCPs, to support their decision to prescribe the product for an individual patient in the context of the approved therapeutic indication(s). The information on clinical efficacy will also be used in the prescriber's communication with the patient about treatment objectives and expected benefits.

Does the proposed wording abide by the following principles?:

* The information should be concise and limited to information relevant to the prescriber.
* Section 5.1 may provide further information on the approved indication (e.g., clarification of what staging system for disease was used), but there should be no reference to “off-label use”.
* Consistency within a class and the therapeutic area is recommended.
* The promotional use of adjectives, adverbs must be avoided, e.g., very strong effect and high affinity. Also, value statements like "clinically relevant" should be avoided.

<Text>

* + 1. <<Patient><and><healthcare provider> engagement>

No applicable for biosimilars.

This section is for completion by the Rapporteurs in cases where there was CHMP early contact with patient organisations and/or healthcare provider organisations.

If no contact, the section can be deleted.

If there was engagement, please summarise the information received. If information was received from both, two separate sub-sections can be created.

<Text>

* + 1. Conclusions

Shortly State comment on key benefits and associated uncertainties. Be explicit on shortcomings of the available data. If the applicant makes claims based on sub-group analyses, these should be preferably prespecified and have a strong biological rationale. State Comment on adequacy of SmPC wordings.

For biosimilars, conclude if the submitted efficacy data support biosimilarity.

<Text>

1. Clinical safety

Please complete section 4 of this report based on eCTD section 2.7.4 “Summary of Clinical Safety” and information from Module 5. Also complete the template tables as reported below. Use of tables for the reporting of data is also encouraged under any of the subheadings. Avoid repetition of the same data between text and tables unless highlighting some qualitative aspects.

For the purpose of this document, the following definitions apply:

‘*Adverse event – AE*’ means any untoward medical occurrence in a subject to whom a medicinal product is administered, and which does not necessarily have a causal relationship with this treatment.

‘*Serious adverse event – SAE*’ means any untoward medical occurrence that at any dose requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death. The definition (in line with ICH E2A) includes important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

‘*Adverse Drug Reaction – ADR*’ means any untoward and unintended response to a medicinal product related to any dose administered, for which, after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

* 1. Safety data collection

Describe how safety data was collected – through diaries, phone calls etc; what was the schedule of safety visits, and what was the follow up; if safety data are pooled the pooling needs to be described.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Was the collection of safety data suitably reliable?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Patient exposure

Please list clinical studies contributing to safety (Cut-off date should be stated).

Please provide numbers and characteristics of included patients (age, stage/severity of disease) and healthy subjects, (could be included in the summary table). The size of the database at X months (X = relevant time period) if appropriate for long-term treatment should be included.

Particularly indicate the safety database for paediatric patients by age groups where appropriate.

Table 12: Patient exposure (cut off)

|  | Patients enrolled | Patients exposed\* | Patients exposed to the proposed dose range | Patients with long term\*\* safety data |
| --- | --- | --- | --- | --- |
| Blinded studies (placebo-controlled) |  |  |  |  |
| Blinded studies (active -controlled) |  |  |  |  |
| Open studies |  |  |  |  |
| Post marketing |  |  |  |  |
| Compassionate use |  |  |  |  |

\* Received at least 1 dose of active treatment

\*\* In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Any information on exposure >12 months should be provided.

Please provide information on any limitations of the safety database in relation to the proposed target population.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Is the safety database considered of sufficient size? Is the length of follow-up sufficient given the intended use of the product?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Adverse events

This section should include adverse events reported during clinical studies with the medicinal product. There are sections dedicated to special populations and drug-drug interactions later in the document, so this section should be based on the integrated summary of safety.

The information should be presented in table format, according to the MedDRA system organ classification. The system organ class (SOC) should be presented and adverse event descriptions should be based on the most suitable representation within the MedDRA terminology. This will usually be at the Preferred Term (PT) Level, although there may be instances where the use of Lowest Term Level or exceptionally group terms, such as High Level Terms may be appropriate. As a general rule, any adverse events should be assigned to the most relevant SOC related to the target organ. For example, PT ‘Liver function test abnormal’ should be assigned to the SOC ‘Hepatobiliary disorders’ rather than to the SOC ‘Investigations’.

The summary table can be the same as in eCTD Table 2.7.4.3. Data should be pooled across studies where possible and appropriate comparisons with placebo or standard of care arms (if available) provided.

The information presented should be factual.

<Text>

* + 1. Adverse drug reactions

Based on the AEs described above, this section should focus on the events where, in accordance with the definition provided at the beginning of section 4., after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

Reversibility of the event should be addressed as appropriate.

Comment on confirmation of non-clinical findings as appropriate.

Possible relationship with manufacturing/quality issues should be mentioned if relevant (e.g. antigenic compounds).

A table format is encouraged and should include a short explanation for the event being classed as ADR.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling. Based on the available list of AEs, are the ADRs proposed justified?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. AEs of special interest, serious adverse events and deaths, other significant events

Please provide a list of AEs of special interest and explain how and why they were chosen as such.

Following the overall safety profile, a separate analysis of the AEs of special interest, the serious adverse events and deaths should be provided.

Results should be presented by the SOC (preferred term) including data on severity of serious adverse events. Summary tables as in eCTD (2.7.4.3 and 2.7.4.6) is necessary.

<Text>

* + 1. ADRs of special interest, serious ADRs and deaths causally related to the medicinal product.

Based on the AEs described above, this section should focus on the events where, in accordance with the definition provided at the beginning of section 4., after thorough assessment, a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility, based for example, on their comparative incidence in clinical trials, or on findings from epidemiological studies and/or on an evaluation of causality from individual case reports.

Reversibility of the event should be addressed as appropriate.

Comment on confirmation of non-clinical findings as appropriate.

Possible relationship with manufacturing/quality issues should be mentioned if relevant (e.g. antigenic compounds).

A table format is encouraged and should include a short explanation for the event being classed as ADR.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling. Based on the available list of AEs of special interest, are the ADRs proposed justified?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Discontinuation due to adverse events

It is important to capture as thoroughly as possible sufficient and detailed information on temporary or permanent discontinuations which are related to adverse events, to enable appropriate assessment of the data. Discontinuations (of treatment or from the study) for reasons not associated to AEs should be presented in section 3.3.1.5.1. (Participant flow) and not here.

It should also be clear whether subjects discontinued treatment or discontinued from the study. It should also be clear which events were AEs and which, if any, were SAEs.

Also, it is important to include information on the need for dose reductions or dose interruptions during the trial - did patients continue therapy but at lower dose due to tolerability issues?

Please describe which events were considered ADRs and the justification for such decision.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling.  Is there any pattern of discontinuations which is concerning, are the numbers of patients that had to dose-modify or discontinue study treatment or the study itself acceptable? Is the choice of ADRs by the applicant adequately justified or should more events be included?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Safety in special populations

Section non applicable to biosimilars.

Please include as many subsections as relevant.

Please include a short summary of all available information both derived from non-clinical and clinical studies in order to substantiate the specific statements in the SmPC (e.g. gender related differences, risks for the use in pregnant women, effect anticipated or observed in children (in the relevant age groups), elderly, etc.). Exposure/response (safety) analyses and graphs may be very informative in this respect (see above).

In general, the wording should be concise and details beyond basic information should only be given when relevant for the critical assessment.

Table 12 and Table 13 below are relevant for the majority of medicinal products: Safety information should be reported specifically for the older population or its lack should be acknowledged.

Please complete the tables below. The columns and rows can be adapted as necessary, but please do not copy pictures from eCTD; the text must be editable. If not relevant, please remove columns for comparator treatments or placebo.

Table 13: AEs by age range

|  | Active | | | | Comparator | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| MedDRA Terms | Age <65  n (%) | Age 65-74  n (%) | Age 75-84  n (%) | Age 85+  n (%) | Age <65  n (%) | Age 65-74  n (%) | Age 75-84  n (%) | Age 85+  n (%) |
| Total AEs |  |  |  |  |  |  |  |  |
| Serious AEs – Total |  |  |  |  |  |  |  |  |
| - Fatal |  |  |  |  |  |  |  |  |
| - Hospitalization/prolong existing hospitalization |  |  |  |  |  |  |  |  |
| - Life-threatening |  |  |  |  |  |  |  |  |
| - Disability/incapacity |  |  |  |  |  |  |  |  |
| - Other (medically significant) |  |  |  |  |  |  |  |  |
| AE leading to drop-out |  |  |  |  |  |  |  |  |
| Psychiatric disorders |  |  |  |  |  |  |  |  |
| Nervous system disorders |  |  |  |  |  |  |  |  |
| Accidents and injuries |  |  |  |  |  |  |  |  |
| Cardiac disorders |  |  |  |  |  |  |  |  |
| Vascular disorders |  |  |  |  |  |  |  |  |
| Cerebrovascular disorders |  |  |  |  |  |  |  |  |
| Infections and infestations |  |  |  |  |  |  |  |  |
| Anticholinergic syndrome |  |  |  |  |  |  |  |  |
| Quality of life decreased |  |  |  |  |  |  |  |  |
| Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures |  |  |  |  |  |  |  |  |
| <other AE appearing more frequently in older patients> |  |  |  |  |  |  |  |  |

Table 14: AE by special population

|  | Active | | | | Comparator | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| MedDRA Terms | Hepatically impaired\*  n (%) | Renally impaired\*\*  n (%) | Pregnant  n (%) | Other  n (%) | Hepatically impaired\*  n (%) | Renally impaired\*\*  n (%) | Pregnant  n (%) | Other  n (%) |
| Total AEs |  |  |  |  |  |  |  |  |
| Serious AEs – Total |  |  |  |  |  |  |  |  |
| - Fatal |  |  |  |  |  |  |  |  |
| - Hospitalization/prolong existing hospitalization |  |  |  |  |  |  |  |  |
| - Life-threatening |  |  |  |  |  |  |  |  |
| - Disability/incapacity |  |  |  |  |  |  |  |  |
| - Other (medically significant) |  |  |  |  |  |  |  |  |
| AE leading to drop-out |  |  |  |  |  |  |  |  |
| <add relevant AE> |  |  |  |  |  |  |  |  |
| <add relevant AE> |  |  |  |  |  |  |  |  |
| <add relevant AE> |  |  |  |  |  |  |  |  |

\* Hepatic impairment is defined as having Child-Pugh score B or C

\*\* Renal impairment is defined as having CKD Stage 3b, 4 or 5 (KDIGO definition)

<Text>

* + 1. ADRs in special populations

Based on the section above, please describe which events were considered ADRs and the justification for such decision.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling.  When assessing data with regard to older adults, not only the number of included patients, but any specific potential risks should be taken into consideration (e.g. cognitive and cardio-vascular effects and influence on renal and hepatic function).  Is the proposed labelling for use in elderly patients of patients with renal or hepatic impairment adequate?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Safety related to drug-drug interactions and other interactions

Section non applicable to biosimilars.

Please mention in this section pharmacokinetic and pharmacodynamic interaction-information directly relevant for safety. Clinically relevant safety experiences obtained from other concomitant use should also be considered.

Specifically reflect on likely co-prescribed medicine classes in the older population.

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Laboratory and other findings

This section should be a short summary of the most important information, not a description of all findings.

Safety laboratory markers may be more sensitive to pick up clinical safety issues (arguably not always specific) or sometimes even predictive of AE.

If relevant, include any finding related, for example to physical examinations (e.g. weight loss).

<Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Post marketing experience

Please identify additional relevant information obtained from post-marketing experience. If none is available, just state “not applicable”.

<Not applicable><Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...) and whether it supports the proposed labelling. Should any post-marketing information be included in the SmPC?  <Not applicable><Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <Not applicable><None><Text> |

* 1. Adverse drug reactions in SmPC

Section not applicable to biosimilars.

The adverse drug reactions included in the SmPC should be described per SOC and their inclusion in the SmPC should be justified.

Please describe the methodology used to define the ADRs proposed for inclusion in the SmPC. If relevant, why were not all AEs considered ADRs? Describe the database used to calculate the frequency and complete Table 15 below.

<Text>

Table 15: ADRs proposed for inclusion in the SmPC

Add/delete rows as required.

|  |  |  |
| --- | --- | --- |
| <System Organ Class> | | Link to data\* |
| Very Common | <Text> |  |
| Common | <Text> |  |
| Uncommon | <Text> |  |
| <System Organ Class> | |  |
| Very Common | <Text> |  |
| Common | <Text> |  |
| Uncommon | <Text> |  |

\* include the link to source data

|  |
| --- |
| (Co)-Rapporteur’s comments:  Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...). Is the list of proposed ADRs in the SmPC duly substantiated? Would you recommend the inclusion of others? Or the exclusion of some?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. In vitro biomarker test for patient selection for safety

If no biomarker test is used, please state “not applicable”.

If applicable, please provide the scientific rationale for the choice of the predictive in vitro biomarker test (e.g. prevalence, relation to disease mechanism).

Analytical method including assay platform, specimen, pre-analytical processing requirements and read-out method.

Analytical and clinical validation strategy:

* Analytical validity: For verifying the suitability of an assay, robustness, accuracy, specificity, sensitivity and linearity should be considered depending on the analytical platform
* Clinical validity (sensitivity/specificity) should be described either by correlation with a clinical endpoint (for novel assays) or –if available- by concordance study with a clinically valid reference assay
* Cut-point selection should be described and discussed in detail since it is of particular importance for the benefit /risk assessment.

<Not applicable><Text>

|  |
| --- |
| (Co)-Rapporteur’s comments:  Note, this is not the “assessment of suitability” of a companion diagnostic, as initiated by a Notified Body. Include specific comments on the data provided (agree/disagree/lack of evidence/strength of evidence/relevance...). Is there sufficient justification for the use of the biomarker for selection of patients based on safety? Is the SmPC text sufficiently clear in this regard?  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

* 1. Overall Rapporteur assessment of clinical safety
     1. Discussion

This section is to be filled by the (Co)Rapporteurs only, not the company.

The contents of this section should be written so that they can be copy/pasted directly to the CHMP AR/Overview.

The discussion is often the most important part of the assessment. In terms of structure it should follow the presentation of the results above.

Try to be as clear and concise as possible (often discussions are too long and verbose, and the true meaning of the data is not addressed).

For each section, the discussion should address the following points:

* Identify the most import findings and deficiencies described above (do not repeat results). Summarise evidence for each conclusion.
* State if the data submitted fulfil the requirements (legal, guidelines, scientific advice)
* What are the “difficult” issues for the CHMP discussion?
* Conclude and state what information should be reflected in the SmPC and the opinion
* What key findings (or uncertainties) should be part of the benefit-risk assessment?

Specific points for discussion:

* Patient exposure: Discuss any limitations of the safety database in relation to the proposed target population. Is there sufficient long-term data?
* Is the safety profile in accordance with that expected from non-clinical studies and known class effects?
* Describe the serious adverse events and whether some patients are particularly at risk? Specific risk factors for the occurrence of adverse drug reactions (dose, duration of exposure, co-morbidity etc.) - Any preventive measure in the SmPC? (monitoring, warning on risk factor etc…).
* Describe relevant safety aspects specific for the paediatric population by age group where appropriate. Link this closely to the recommendations in the SmPC. Are there any specific (serious) ADRs and/or monitoring requirements?

Additional considerations:

- is there a need to convene a SAG?

- is there a need to trigger an inspection?

For biosimilars:

* Discuss the results of the comparison of the most important adverse drug reactions (type, severity and frequency). Describe the safety concerns that have been observed or that are otherwise of concern even if (yet) unobserved for the biosimilar candidate. If no confirmatory clinical study has been conducted, discuss the available data from which a similar safety profile could be inferred. Compare the immunogenicity profile of the biosimilar candidate and the reference product. If no human immunogenicity data have been generated, discuss the available data from which a similar immunogenicity profile could be inferred.
* Discuss available data questioning biosimilarity (e.g. differences observed at quality, non-clinical level) which could have an impact on safety/immunogenicity and/or differences observed at clinical level such as higher incidence of certain adverse events, new signal or new adverse events that were not observed for the reference product. Discuss any specific risks anticipated for the biosimilar e.g. possible safety concerns that may result from a manufacturing process different from that of the reference product, especially those related to infusion-related reactions and immunogenicity.

<Text>

* + - 1. <Additional safety data needed in the context of a <conditional> MA <under exceptional circumstances>>

The recommendation to grant a marketing authorisation under exceptional circumstances by the CHMP should carefully be considered for situations where, for a number of reasons, it does not seem possible to ever assemble a “full” dossier. Notably, a marketing authorisation under exceptional circumstances will normally remain under exceptional circumstances and not lead to a conversion into a normal marketing authorisation.

Describe here the missing data in Module 5, why it is missing (rarity of disease = exceptional, early development = conditional) and how the gap is foreseen to be bridged, i.e. which data is required to be submitted.

In case conditions for Annex II in relation to the <conditional> MA <under exceptional circumstances> have been identified, use the following statement:

<The following measures are necessary to address the missing safety data in the context of a <conditional> MA <under exceptional circumstances>:>

<Text>

* + 1. Product information

Comments and edits can be made directly on the annexes and do not need to be repeated here. Use this section for a more general assessment of the adequacy of the proposed SmPC.

How are the findings (or lack of information) reflected in the SmPC? Ensure correspondence with SmPC (e.g., sections 4.3 contraindications, 4.4 special warnings, 4.7 Effects on ability to drive and use machines 4.8 Undesirable effects, 4.9 Overdose, as appropriate) and that all information in the SmPC is explicitly assessed and supported by the scientific assessment.

<Text>

* + 1. Conclusion

A brief statement about the conclusions that can be drawn from the clinical safety documentation should be provided here (e.g., most frequent adverse drug reactions and other significant safety issues).

Comment also on which safety findings should be considered for inclusion in the safety specification of the RMP.

For biosimilars, conclude if the submitted safety data support biosimilarity.

<Text>

1. Risk management plan

The safety specification in the RMP is assessed and agreed by CHMP/CAT.

* 1. Summary of safety concerns

Please copy/paste the proposed “Summary of safety concerns” table from the RMP (Table SVIII.1). Please be mindful not to include any Personal Data (e.g. patient identifiers).

Include a very brief justification for each. If there are none, please state why there are no safety concerns related to the product.

Table 16: Summary of safety concerns in proposed RMP

| Summary of safety concerns | |
| --- | --- |
| Important identified risks | <List> |
| Important potential risks | <List> |
| Missing information | <List> |

<Text>

|  |
| --- |
| (Co)-Rapporteur’s Comments:  The contents of this section should be written so that they can be copy/pasted directly to the CHMP AR/Overview.  It is important to only comment if there are major errors/inconsistencies in the safety specifications in the RMP from the Applicant or if the information in it is not in line with the clinical assessment. This is particularly important if comments lead to requests for an updated version of this section of the RMP and if the comments impact for example the summary of the RMP. Otherwise, simply say that the presentation in the RMP is largely acceptable.  To establish the **list of important identified and potential risks** for inclusion, please consider the following questions:   * If further characterised and if confirmed, would this important or potential risk have an impact on the risk-benefit balance of the medicinal product? * Would the important or potential risk have clinical consequences? Please try not to use the System Organ Class “Investigations”. Is there an outcome of interest? * What is the relation to severity of condition? * What is the target population? There is no need to consider risks that will not affect the indicated population. * What are the clinical practices? no need to consider risks for which risk minimisation measures have become established in clinical practice.   Please also consider that an important identified risk would usually warrant further evaluation as part of the pharmacovigilance plan and risk minimisation activities. An important potential risks would usually require further evaluation as part of the pharmacovigilance plan.  To establish the **list of Missing information**, please consider the below:   * Absence of safety data in a defined population * Evidence of a potential concern in the said population. * Always has to be relevant for the approved indications   e.g. Missing information in children should not be part of the List of Safety Concerns if product is not authorised in this population  Please consider option of **Potential risk of [important safety issue] in off-label paediatric** use if **all** below are true:   * There is a high probability of the product being used off-label children * There is a documented risk for this population (e.g. this may have led to the product not being approved in children) * The risk is not present in the approved population (i.e. is not already included in the safety profile) * The risk is important (i.e. risk-benefit impact, if only at individual level, as formal risk-benefit analysis might not have been performed in this population).   Include a discussion of the **potential for misuse for illegal purposes** if applicable.  <Text>  Resulting questions:  Any questions can be written here and then transferred into the List of Questions in the CHMP AR/Overview. Mark the question as MO or OC as relevant.  Please focus the questions on issues that, if not addressed, would have a direct impact on the Benefit/Risk evaluation, the SmPC text, the likelihood of inspection, etc. Avoid “nice-to-have” questions.  <None><Text> |

1. Pharmacovigilance system

Rapporteurs to choose one of the following and delete the rest.

<The (Co)-Rapporteur considers that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.>

<The (Co)-Rapporteur, having considered the data submitted in the application was of the opinion that it was not appropriate to conclude on pharmacovigilance system at this time.><See list of questions>.

<The (Co)-Rapporteur, having considered the data submitted in the application was of the opinion that a pre-authorisation pharmacovigilance inspection is required>.

<Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the CHMP may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market>

(Co)-Rapporteur’s comments

<No comments> <Text>

1. List of references

To be completed by the applicant (if they agreed to pre-fill the template).

Assessors can include additional references if needed.

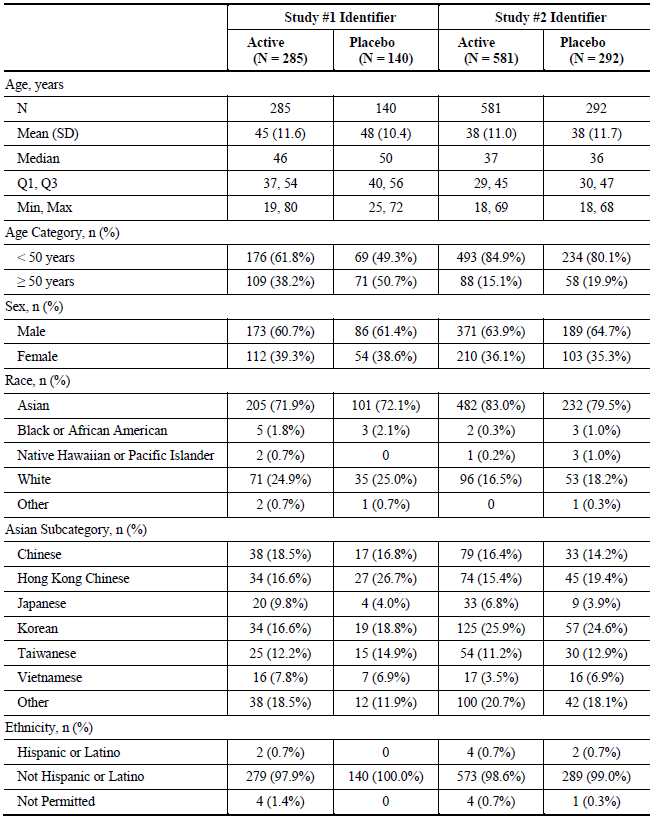
<Text>

Note: it was agreed by both the drafting group and the steering group that there should be no list of questions here. All questions should be added directly to the Overview instead.

1. Annex I (please delete when report finalised)
   1. Examples of tables for baseline data

The variables included will depend on the study design, population, and intended indication.

Demographic and baseline characteristics:



Baseline disease characteristics:

