XX September 2023

Parallel EMA/EUnetHTA 21 Joint Scientific Consultation

Briefing document template

[Standard headings in the template should be used whenever possible; if it is considered necessary to deviate from the pre-specified headings to accommodate product-specific requirements, alternative or additional headings/sections may be considered.

This annotated template should be read in conjunction with the relevant guidelines that can be found on the website of the European Medicines Agency and of EUnetHTA 21:

- European Medicines Agency Guidance for applicants seeking scientific advice and protocol assistance - EMA/4260/2001
- EUnetHTA 21 and European Medicines Agency Guidance on Parallel EMA/EUnetHTA 21 Joint Scientific Consultation - EMA/410962/2017 Rev.6

Bracketing convention: {text}: Information that is required to be filled in; <text>: Text to be selected or deleted as appropriate.

[Text] is for explanation and guidance.

Formatting convention: Verdana 9 pt., single space, justified.

References convention:

- For citation of literature references, footnotes are preferred, alternatively the format (first author <et al.>, publication year) is recommended.

The Applicant must ensure that if different consultation formats are used consecutively (e.g. regulatory advice before parallel JSC), the content of the consultation does not lead to a duplication of the advice for participating agencies.

This template can also be applied for HTA-only Joint Scientific Consultations (JSC). In this case all references to Regulator's engagement are not applicable.]

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Invented Name:	*{}*
Active substance:	*{}*
Pharmaco-therapeutic group:	*{}*
Intended indication(s):	*{}*
Applicant:	*{}*
Version:	*{}*
Date:	*{DD/MM/YYYY}*

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List of Figures

List of Tables

List of Abbreviations

[Any acronyms or abbreviations used should also be defined the first time they appear in the text.]

Summary

[It is strongly recommended to address all elements outlined below (whenever applicable) for any Parallel EMA/EUnetHTA 21 Joint Scientific Consultation (JSC) request, regardless of the scope of the questions. This summary will inform the background information section of the final advice letter of the European Medicines Agency and the Final Written Recommendation of EUnetHTA 21. An upper limit of 3 pages for the summary is recommended.]

1. Background information

1.1. Background information on the disease to be treated

[Outline main features of the disease including relevant aetiology, epidemiological data, information on natural history of the disease and evolution of disease symptoms and burden. Evolution of treatment should be discussed, including current standard therapy (referencing relevant guidelines and variations between the countries) and referring to relevant publications as well as any current unmet need(s). For reimbursement decisions, the availability of treatment alternatives is a critical issue. Thus, a solid discussion of all technologies (drugs, devices, procedures) that present relevant alternatives for the treatment of the pathology (stage, line of treatment) together with their labelling status in Europe and North America. In the case of the existence of new treatments that are in advanced phases of development including compassionate use programmes, this information should be included. This summary will inform the background information section of the Final Written Recommendation of EUnetHTA 21.]

1.2. Indication

[Specify the indication(s) intended for the label including product positioning in the treatment pathway: (e.g. 1st line, 2nd line, 3rd line, add-on, monotherapy, screening pre-treatment, monitoring during treatment, etc.). Describe whether it is a combination or monotherapy. Aim of treatment (preventive, curative, palliative, symptomatic, disease modifying). Target population should be described as precisely as possible. If any population should not be included in the label, this should be clearly indicated.]

1.3. Background information on the product

[Include mode of action, chemical structure and pharmacological classification.]

1.3.1. Characteristics of the product

[Chemical/biological product; orphan product; advanced therapy medicinal product; Application together with a medical device, companion diagnostic or artificial intelligence; any special precautions or recommendations for use of the product (including a possible risk management strategy).]

1.3.2. Form, route of administration, dose, dosage

[Route of administration and the pharmaceutical form of the product should be described. Dose, frequency of administration and the duration of use should be discussed based on the available evidence at the stage of development.

If the administration of the product is associated with the use of a diagnostic test, a medical device or with a medical procedure, this information should be stated, and adequate information given on the associated test or device.]

1.4. <Quality development>

[Relevance and level of detail included may vary depending on the scope of the request. Special pharmaceutical aspects, if any, e.g. novel delivery system, etc.]

1.5. <Non-clinical development>

[Relevance and level of detail included may vary depending on the scope of the request. Proof-of-concept and main toxicological findings could be informative.]

1.6. Clinical development

[Introduce and describe the status of the clinical development programme. A tabulated summary of completed, ongoing and planned clinical trials as well as post-launch evidence generation (if any planned) could be informative.

Briefly summarise the following aspects:

If scientific advice has been previously requested from the CHMP, national or non-EU Authorities (e.g. FDA).

If scientific consultation has been previously requested from national HTA bodies or EUnetHTA (21). If yes, please include the full advice documents as an annex to your briefing document.

Indicate if relevant CHMP guidance/CHMP advice has been followed or if any deviations have been made or proposed.

Indicate applicability and status of the Paediatric Investigation Plan (with or without deferral or waiver). Indicate availability and need for development in other special populations such as the elderly, male/female and ethnic minorities.

Present the study protocol that is the subject of the Parallel EMA/EUnetHTA 21 JSC (study design, inclusion and exclusion criteria, comparator, endpoints, patient reported outcomes (PRO), sample size estimation, statistical analyses, etc.).

Explain the choice of PROs and patient reported outcome measures (PROMs) including a literature review of existing PROs in the disease along with justification of the appropriateness of the questionnaire(s)

chosen and the frequency of collection of this data. If patient preference data are planned to be collected alongside clinical development, detailed methodology should be given.

Provide minimum information on post-launch evidence generation (if planned) for which the developer also requests advice, i.e. anticipated gaps, remaining research questions, high level design of the study, core data set and data source details if use of an existing data source is planned.]

1.7. Regulatory status

[Describe the worldwide Regulatory status of the product (e.g. any existing marketing authorization (MA), or planned marketing authorization application (MAA) timelines), indicating planned type and timelines of MAA (e.g. full/mixed dossier; advanced therapy, biosimilar, generic/hybrid/ product) or variation.

If the product has received Orphan Drug Designation (ODD) related to the intended indication, state the orphan indication, the criteria on which the ODD was based and, if applicable, the development plan to support similarity or clinical superiority claims. Clarify whether the product was granted eligible for the PRIME (priority medicines) scheme launched by the European Medicines Agency.]

1.8. Rationale for seeking parallel consultation

[Describe the scope of the questions and the rationale for the Parallel EMA/EUnetHTA 21 JSC request (e.g. clinical/non-clinical/quality/significant benefit/similarity/conditional approval/exceptional circumstances).]

1.9. Product value proposition

[Describe value propositions with clear statement on drug positioning in the treatment pathway and how the trial evidence will be used to support these.]

2. Questions and Applicant's positions

[**Questions** should conform to the **scope** of the Scientific Advice/Protocol Assistance procedure (EMA/4260/2001). It is recommended that questions are phrased in a way to allow for an unambiguous understanding of the question. The scope should be carefully considered in order to avoid too broad or too narrow questions. For a given development program, it is recommended that clinical questions are posed about population, comparator and outcome. The intended place in treatment of the intervention should be clear.

The wording of the question should be clear and concise, avoiding extended reference to the justifications (which should be discussed in the Applicant position) and starting with e.g. "Does the CHMP agree that/with …?" OR "Do HTA bodies agree that/with…?". Both EMA and EUnetHTA 21 reserve the right to answer selected questions that have been directed to the other entity if deemed appropriate. Questions concerning the future appraisals and/or reimbursement/coverage decision will not be considered by HTA bodies, in accordance with the general principles of Parallel EMA/EUnetHTA 21 JSC (see the Guidance for Joint Scientific Consultations). Furthermore, as the existence of a medical need is included in the Committee for Scientific Consistency and Quality (CSCQ) eligibility assessment for Parallel EMA/EUnetHTA 21 JSC, related questions are out of the scope of Parallel EMA/EUnetHTA 21 JSC.

It is recommended that the number of questions be limited (10 maximum) in order to focus the discussion on the relevant aspects of the dossier. It is highly recommended to ask focused questions with a maximum of one or two sub-questions.

Questions should be ordered in the corresponding section according to the expertise (also multidisciplinary) required for the assessment and numbered sequentially.

IMPORTANT INFORMATION

Each question should be followed by a corresponding, separate Applicant's position including a comprehensive justification of the chosen approach.

All key information about the topic should be sufficiently discussed, so that the Applicant's position can function as a 'stand-alone' justification. Issues to be covered could include the following: context and proposal, other options (potentially) considered together with a critical discussion on the relative merits and drawbacks of various approaches, possible consequences and eventual measures to ameliorate these. In general, an extension of 1 to 3 pages for each Applicant position is recommended.

Cross-references to the relevant parts of the briefing document or annexes can be included if additional detail is needed to support the case.]

2.1. <Questions on Chemical, Pharmaceutical and Biological development>

Question 1

{}?

Applicant's position

{}

Question 2

{}?

Applicant's position

{}

2.2. <Multidisciplinary Question<s> on Chemical, Pharmaceutical, Biological and Toxico-Pharmacological development>

Question {X}

{}?

Applicant's position

{}

2.3. <Questions on Toxico-Pharmacological development>

Question {X}

{}?

Applicant's position

{}

2.4. <Multidisciplinary Question<s> on Toxico-Pharmacological and Clinical development>

2.5. Questions on Clinical development

[There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA. Proposed areas are the following:

- Population, including potential deviation between study population vs targeted indication, biomarkers, subgroups, extrapolation, generalizability;

- Intervention, including dosing, concomitant, add-on, monotherapy, duration, label/indication induction, life-long therapy;
- Comparator;
- Outcomes, including primary & secondary endpoints, PROs, Adverse Events (AEs);
- Study Design, including randomisation, duration, statistical methods, time point frequency of data collection.

The topics listed above are essential for the discussion with HTA bodies. Therefore, justified proposals for each of them should appear in the Applicant's position if they are to be discussed during the meeting. Otherwise, they should be clearly stated in section 3.3.1 Planned clinical trials.]

2.5.1.< Regulatory questions>

Question {X}

{}

Applicant's position

2.5.2.<Regulators' & EUnetHTA 21 Questions>

[Please note that there is no option for a follow-up consultation with EUnetHTA 21 during the project phase. All relevant questions must be submitted in this briefing document.

Questions should be presented following the topics as described above.]

Questions regarding population

Question {X}

{}

Applicant's position

{}

Questions regarding intervention

Question {X}

{}

Applicant's position

{}

Questions regarding outcomes

Question {X}

{}

Applicant's position

{}

Questions regarding study design

Question {X}

{}

Applicant's position

{}

2.5.3.< Questions regarding HTA>

[There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA. Proposed areas are the following:

- Population, including potential deviation between study population vs targeted indication, biomarkers, subgroups, extrapolation, generalizability;
- Intervention, including dosing, concomitant, add-on, monotherapy, duration, label/indication induction, life-long therapy;
- Comparator;
- Outcomes, including primary & secondary endpoints, PROs, Adverse Events (AEs);
- Study Design, including randomisation, duration, statistical methods, time point frequency of data collection.

The topics listed above are essential for the discussion with HTA bodies. Therefore, justified proposals for each of them should appear in the Applicant's position if they are to be discussed during the meeting. Otherwise, they should be clearly stated in section 3.3.1 Planned clinical trials.]

Questions regarding population

Question {X}

{}

Applicant's position

{}

Questions regarding intervention

Question {X}

{}

Applicant's position

{}

Questions regarding outcomes

Question {X}

{}

Applicant's position

{}

Questions regarding study design

Question {X}

{}

Applicant's position

{}

2.5.4.<Questions on Significant Benefit>

[For Protocol Assistance, the questions should be within the scope of the designated orphan indication. See EMA Guidance for Companies requesting Scientific Advice or Protocol Assistance' (EMA/4260/2001).]

Question to the COMP {X}

{}

Applicant's position

{}

2.6. Questions on Post-Launch Evidence generation (PLEG)

[There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA assessment. Proposed areas are the following:

- *Anticipated evidence gaps and unanswered research questions at the end of pivotal trials*
- *Post-launch study design with minimum information on additional data planned to be collected e.g. population targeted, comparative data, choice of outcomes, timeframe*
- *Quality of data source if the study is based on a disease registry or other existing database. For discussion on quality of disease registry, it is recommended to refer to REQueST (Registry Evaluation and Quality Standards Tool) developed by EUnetHTA, which covers all important aspects related to the quality of registries* https://eunethta.eu/request-tool-and-its-vision-paper/

Please note, discussions on PLEG can be facilitated only in conjunction with a request for discussion of pivotal trial design and when contextualized with clinical data from the pivotal (phase II/III) studies.]

Question {X}

{}

Applicant's position

{}

3. Product development program

[This section should give a comprehensive scientific overview of the product development program, providing relevant systematic information in sufficient detail, together with a critical discussion. However, it should be kept in mind that any information essential for the justification of a given question should also be sufficiently discussed in the corresponding Applicant's position. The proposed list of subsections is neither meant to be exhaustive nor mandatory, since the relevance or applicability of each subsection may vary depending on the scope of the parallel consultation request. In this respect, the potential direct or indirect relevance of the information covered in relation to the questions posed should be considered. Additional details can be included in study protocols, study reports, investigators' brochure provided as annexes with cross-references in the background information and relevant Applicant Position. The use of tabulated overviews and graphs is encouraged.]

3.1. Quality background information

<Active substance>

<Finished product>

3.2. Non-clinical background information

[It is recommended to include a tabulated overview of all non-clinical studies (completed, ongoing and planned), including study number, main design features and GLP status. Main findings and safety margins may be described in the narrative.]

<Pharmacology>

<Pharmacokinetics>

<Pharmacodynamics>

<Toxicology>

3.3. Clinical background information

[A tabular overview of all clinical studies (completed, ongoing and planned), including study number, main design features, patient number and characteristics, design, doses and duration of treatment, comparator, results of the trial (or preliminary results of ongoing trials if available) etc. could be informative, if not provided elsewhere. Detailed information should be available in study reports in annexes. Cross-links to annexes are recommended. Whilst the focus should be kept on the intended indication, the development in other indications could be briefly summarised, where relevant. Data of early phases are also necessary as they serve as basis of the development plan.]

<Clinical pharmacology>

<Pharmacokinetics>

<Pharmacodynamics>

<Clinical efficacy>

3.3.1.Planned clinical trials

[This section should provide a comprehensive overview of all planned trials with the product in the intended indication. For the trial that is to be the subject of the parallel consultation, a rationale and a synopsis of the protocol should be provided. The synopsis should contain key information on objectives of the trial, trial design, patient population (inclusion and exclusion criteria), patient subgroups and stratification (if applicable), line of treatment, comparators, endpoints (primary, secondary, etc.), measures used to assess endpoints, flowchart, follow up, methods of statistical analysis etc. All relevant systematic information should be given at a sufficient level of detail, together with justification for the choices made and a critical discussion of key issues.]

3.3.2.Overview of the clinical development program

[A general overview of the clinical development program should be based on a comprehensive discussion of e.g. the main clinical results so far, dose-response, exploratory trials, special populations, supportive and pivotal clinical studies, and any analyses performed across trials (pooled and meta-analysis).

The discussion should identify the most important findings and challenges in the clinical development program and its compliance with legal requirements, relevant clinical guidelines, previous scientific consultation (sufficiently justifying any deviations), etc. Information on the geographical distribution of centres participating in the pivotal clinical studies can be reflected in this section.]

3.3.3.Clinical efficacy

[A general overview of the clinical development program should be based on a comprehensive discussion of e.g. the main clinical results so far, dose-response, exploratory trials, special populations, supportive and pivotal clinical studies, and any analyses performed across trials (pooled and meta-analysis). The discussion should identify the most important findings and challenges in the clinical development program, and its compliance with legal requirements, relevant clinical guidelines, previous scientific consultation (sufficiently justifying any deviations), etc. Information on the geographical distribution of centers participating in the pivotal clinical studies can be reflected in this section.]

3.3.4.Clinical safety

[A general overview of the safety profile of the product should be based on a comprehensive discussion of e.g. patient exposure (safety database), adverse events observed so far, serious adverse events and deaths, laboratory findings, safety-related discontinuations, specific safety findings, immunological events, safety in special populations, etc.]

3.4. Information for HTA

3.4.1.<Relative effectiveness>

[Guidance on consideration of relative effectiveness evidence should be brought together in a separate section before the section on economic evaluation plans and is optional. However, it is very likely that

the generation of evidence on relative effectiveness (based on clinical trial efficacy) will be discussed as part of the consultation. The section could mention (as bullets):

<Population>,

<Choice of comparator>,

<Study design>,

<Study duration>,

<Evidence synthesis (including indirect comparisons/NMA)>,

<Trial endpoints (including minimal clinically important differences)>,

<Predictive modelling of effectiveness from surrogate endpoints>,

<Transferability of trial data>,

<Evidence for sub-groups>,

<Other relevant statistical issues (e.g. stratification)>,

<Choice of measures of health-related quality of life could be included in this section>,

[PAES studies are in scope (ll97-98) and therefore plans and study designs for 'real world' evidence generation post-launch (potentially pre-launch) to verify trial-based estimates of effectiveness, whether or not PAES, merit (separate) mention in this briefing document (optional).]

4. Health economic assessment (optional)

Disclaimer: As economic/pharmacoeconomic assessment falls within the scope of neither Joint Clinical Assessment (JCA) nor Joint Scientific Consultation (JSC) under Sections 1 and 2 of Chapter II of the HTA Regulation, advice on "health economic assessment" is hereby provided as part of the voluntary cooperation on health technology assessment according to Article 23 of the EU HTA Regulation.

4.1. Questions and Applicant's positions

4.1.1. Health economic assessment questions

[There are no mandatory areas for discussion. However, several areas are recommended based on their importance for HTA assessment. Proposed areas are the following:

- Population
- Choice of comparator
- Model structure
- Model assumption and planned scenario model outcomes
- Clinical data and other data sources used to populate the model
- Time horizon and extrapolation hypothesis
- Perspective (societal, healthcare related etc.)
- Utility values
- Collection of resource utilisation data
- External validity

The topics listed above are essential for the discussion with HTA bodies. Therefore, justified proposals for each of them should appear in the Applicant's position if they are to be discussed during the meeting. Otherwise, they should be clearly stated in section 3.3.1 Planned trials.]

Question {X}

{}

Applicant's position

{}

4.2. Product development program

4.2.1. Information on health economic assessment for HTA

[The Applicant should state the scope of the planned economic analysis, clearly defining the research questions. Evidence gaps and model assumptions should be described. In this section the external validity needs to be explored.

If plans for the economic evaluation are provided, these should include to the extent possible:

<• Description of the proposed model (diagram, modelling approach, time horizon, perspective)>

<• Data collection plans to inform the model:

- Evidence synthesis/meta-analysis – sources of evidence

- Comparators – MTC and indirect comparisons and evidence available

- Trial endpoints used to derive health outcomes in the model

- Quality of life – source and methods, tools used to measure quality of life

- Incorporation of adverse effects

- Resource use – sources and methods, tools used to measure resource utilisation>

<• Methodological Approaches:

- Extrapolation – assumptions and data sources

- Continuation rules

- Use of surrogate outcomes

- Planned sensitivity analyses

- Expected (key) limitations

<• *External validity>]*

List of References

[In general, any potentially relevant publications included in the list of references should be annexed (in .pdf format, either collated as a single document or, if provided as single files, clearly identified and whenever possible compiled in one or more compressed files, for convenience). In case a relevant publication is not included at the time of validation, it should be ensured that it can be made available upon request.]

List of Annexes

[Annexes should include any information potentially relevant to the questions, e.g.

Investigators' brochure

Study protocols (final, draft or outline/synopsis)

Study reports (final/draft/synopses)

Previous scientific advice received (e.g. CHMP Scientific Advice/Protocol Assistance, any relevant official correspondence and meeting minutes with National Competent Authorities in EU-Member States, FDA and other non-EU Authorities as well as with national HTA bodies or joint EMA/HTA advice)

Relevant guidelines (non-EMA)

Documents related to Orphan Drug Designation (e.g. COMP summary report)

Documents relating to Marketing Authorisation Application e.g. Day 120 List of Questions, Letter of undertaking.

Documents related to Paediatric Investigation Plans (e.g. PDCO summary report, opinion)

Contract/agreement consultant/CRO - sponsor

Literature references]

Contact points

Any question or comment concerning this document or any other point related to the Parallel EMA/EUnetHTA 21 JSC should be sent to EUnetHTA21-JSC@g-ba.de and scientificadvice@ema.europa.eu.