18 February 2015
EMA/COMP/780484/2014 Rev. 1
Procedure Management and Business Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes of the 7-9 January 2015 meeting

Some documents mentioned in the agenda/minutes cannot be released at present within the framework of Regulation (EC) No 1049/2001 on access to documents because they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1 Adoption of the agenda, EMA/COMP/777792/2014

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 9-11 December 2014 EMA/COMP/727397/2014

The minutes were adopted via written procedure.

1.3 Declaration of conflicts of interest

In accordance with the Agency's Policy and Procedure on the handling of conflicts of interests, participants in this meeting were asked to declare any conflict of interests on the matters for discussion (in particular any changes, omissions or errors to the already declared interests). No new or additional conflicts of interest were declared.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Chimeric group B adenovirus (11p/3) with deletions in the E3 and E4 regions for treatment of ovarian cancer, PsiOxus Therapeutics Ltd - EMA/OD/211/14
[COMP coordinator: B. Bloechl-Daum]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The sponsor proposed a new mode of action which they believe will offer a clinically relevant advantage to support the significant benefit.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preclinical in vivo study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. This should be done within the context of the current European Guidelines for the condition.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor further elaborated on the issue of significant benefit. In particular, the sponsor discussed data from a preclinical model of the condition where treatment with the proposed product in combination with paclitaxel resulted in improved reduction of tumour burden compared to paclitaxel alone. The Committee agreed that the condition, ovarian cancer, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing chimeric group B adenovirus (11p/3) with deletions in the E3 and E4 regions was considered justified based on a preclinical model of the condition showing reduction of tumour burden.

[1] The procedures under assessment discussed by the COMP are considered confidential. COMP meeting reports and subsequent minutes will contain additional details on these procedures once these are finalised. Access to documents in relation to these procedures is possible after marketing authorisation is granted according to the Agency policy on access to documents (EMA/127362/2006).

The condition is chronically debilitating in particular due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years.

The condition was estimated to be affecting less than 3 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing chimeric group B adenovirus (11p/3) with deletions in the E3 and E4 regions may be of significant benefit to those affected by the condition. The sponsor has provided data in preclinical settings that support improved effects in reduction of tumour burden compared to existing treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for chimeric group B adenovirus (11p/3) with deletions in the E3 and E4 regions for treatment of ovarian cancer, was adopted by consensus.

2.1.2 Product for treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma - EMA/OD/208/14

[COMP coordinator: F. Naumann-Winter]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was asked to describe and justify the methodology used for the prevalence calculation.

The sponsor was asked to justify:

a) the appropriateness of the epidemiological index used, based on the duration of the condition at the time the application is made;

b) the inclusion/choice of the sources selected for the estimation of the prevalence of the condition.

The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor further discussed their position on the issue of prevalence. It was stated that since complete prevalence data for CLL/SLL had not been identified, indirect approaches were needed to calculate the prevalence. The sponsor assumed that SLL accounted for approximately 25% of all CLL/SLL cases, used different registries (such as Haemacare, Itacan, HMRN), and provided several 5, 10 and 20 year partial prevalence figures according to different databases. The sponsor also acknowledged that there has been an increase of the duration of the disease in the last decades, but argued that the new treatment options are not yet reflected in population based prevalence estimates.

The COMP noted that the sponsor had not provided new data or analyses in their responses, and that considerable uncertainty still remained. In particular, the latest median survival referred to dates back

15 years, and a clear duration of the condition at the time the application was made was missing. Moreover, there is considerable variability between different databases used, which increases uncertainty. Therefore, it was difficult to consider that the prevalence criterion had been justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2015, prior to final opinion.

2.1.3 Product for treatment of N-acetylglutamate synthase deficiency - EMA/OD/227/14

[COMP coordinators: L. Greene/ V. Tillmann]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of N-acetylglutamate synthase (NAGS) deficiency, the sponsor was asked to further elaborate on:

  - the pharmaceutical characteristics of the product, in particular pharmacokinetics, stability and compatibility with food or beverages;
  - the excipients and the potential safety concerns for infants and children in this regard.

In the absence of data, medical plausibility of the proposed product, in particular with regards to the proposed formulation, cannot be assessed.

- Significant benefit

The arguments on significant benefit were based on a major contribution to patient care and the potential improved safety in the condition.

The sponsor was requested to further discuss the argument on a major contribution to patient care based on results from any available study or clinical experience with the proposed product documenting patients' experience, e.g. in the context of a validated questionnaire, to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor was also requested to elaborate in more detail on the claimed safety concerns with authorised medicinal products based on available literature.

Without this requested data significant benefit of the proposed product cannot be assessed.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor elaborated on bibliographical data on the pharmaceutical characteristics of the product and compatibility with different foods. The sponsor however did not present any data with the product in either preclinical models or patients affected by the condition. The COMP considered that in the absence of data with the product, the criteria for designation cannot be justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2015, prior to final opinion.

2.1.4 Product for treatment of hyperornithinaemia, hyperammonaemia, homocitrullinuria syndrome - EMA/OD/228/14

[COMP coordinators: L. Greene/ V. Tillmann]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

The COMP considered that the condition originally proposed by the sponsor should be renamed as "ornithine translocase deficiency (hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome" based on the currently used nomenclature in the scientific community.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of ornithine translocase deficiency (hyperornithinemia-hyperammonemia-homocitrullinuria (HHH) syndrome, the sponsor was asked to further elaborate on:

- the pharmaceutical characteristics of the product, in particular pharmacokinetics, stability, and compatibility with food or beverages;
- the excipients and the potential safety concerns for infants and children in this regard.

In the absence of data, medical plausibility of the proposed product, in particular with regards to the proposed formulation, cannot be assessed.

- Number of people affected

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

Although it is acknowledged that epidemiological data on the proposed condition is scarce it is the responsibility of the sponsor to propose an estimate reflecting as close as possible the prevalence of the condition in the European Union based on available literature or patients registers.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor elaborated on bibliographical data on the pharmaceutical characteristics of the product and compatibility with different foods, but did not present any data with the product in either preclinical models or patients affected by the condition. Furthermore, a prevalence of 0.09 in 10,000 was proposed as the most conservative estimate in Europe. The COMP was of the opinion that in the absence of data with the product in the condition orphan designation cannot be granted.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2015, prior to final opinion.

2.1.5 Product for treatment of argininosuccinate lyase deficiency - EMA/OD/230/14

[COMP coordinators: L. Greene/ V. Tillmann]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

The COMP considered that the condition originally proposed by the sponsor should be renamed as "Argininosuccinic aciduria" based on the currently used nomenclature in the scientific community.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Argininosuccinic aciduria, the sponsor was asked to further elaborate on:

- the pharmaceutical characteristics of the product, in particular pharmacokinetics, stability, and compatibility with food or beverages;
- the excipients and the potential safety concerns for infants and children in this regard.

In the absence of data, medical plausibility of the proposed product, in particular with regards to the proposed formulation, cannot be assessed.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor elaborated on bibliographical data on the pharmaceutical characteristics of the product and compatibility with different foods. The sponsor however did not present any data with the product in either preclinical models or patients affected by the condition. The COMP considered that in the absence of data with the product, the criteria for designation cannot be justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2015, prior to final opinion.

2.1.6 Product for treatment of lysinuric protein intolerance - EMA/OD/232/14

[COMP coordinators: L. Greene/ V. Tillmann]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of lysinuric protein intolerance, the sponsor was asked to further elaborate on:

- the pharmaceutical characteristics of the product, in particular pharmacokinetics, stability, and compatibility with food or beverages;
- the excipients and the potential safety concerns for infants and children in this regard.

In the absence of data, medical plausibility of the proposed product, in particular with regards to the proposed formulation, cannot be assessed.

- Number of people affected

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

Although it is acknowledged that epidemiological data on the proposed condition is scarce it is the responsibility of the sponsor to propose an estimate reflecting as close as possible the prevalence of the condition in the European Union based on available literature or patients registers.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor elaborated on bibliographical data on the pharmaceutical characteristics of the product and compatibility with different foods, but did not present any data with the product in either preclinical models or patients affected by the condition. Furthermore, a prevalence of 0.49 in 10,000 was proposed as a conservative estimate in Europe. The COMP was of the opinion that in the absence of data with the product in the condition orphan designation cannot be granted.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2015, prior to final opinion.

2.1.7 Product for treatment of arginase deficiency - EMA/OD/231/14

[COMP coordinators: L. Greene/ V. Tillmann]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

The COMP considered that the condition originally proposed by the sponsor should be renamed as "argininaemia" based on the currently used nomenclature in the scientific community.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of argininaemia, the sponsor was asked to further elaborate on:

- the pharmaceutical characteristics of the product, in particular pharmacokinetics, stability, and compatibility with food or beverages;
- the excipients and the potential safety concerns for infants and children in this regard.

In the absence of data, medical plausibility of the proposed product, in particular with regards to the proposed formulation, cannot be assessed.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor elaborated on bibliographical data on the pharmaceutical characteristics of the product and compatibility with different foods. The sponsor however did not present any data with the product in either preclinical models or patients affected by the condition. The COMP considered that in the absence of data with the product, the criteria for designation cannot be justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2015, prior to final opinion.

2.1.8 Product for treatment of carbamoylphosphate synthetase I deficiency SA - EMA/OD/233/14

[COMP coordinators: L. Greene/ V. Tillmann]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of carbamoyl-phosphate-synthase-1 deficiency a, the sponsor was asked to further elaborate on:

- the pharmaceutical characteristics of the product, in particular pharmacokinetics, stability, and compatibility with food or beverages;
- the excipients and the potential safety concerns for infants and children in this regard.

In the absence of data, medical plausibility of the proposed product, in particular with regards to the proposed formulation, cannot be assessed.

- Significant benefit

The arguments on significant benefit were based on a major contribution to patient care and the potential improved safety in the condition.

The sponsor was requested to further discuss the argument on a major contribution to patient care based on results from any available study or clinical experience with the proposed product documenting patients' experience, e.g. in the context of a validated questionnaire, to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor was also requested to elaborate in more detail on the claimed safety concerns with authorised medicinal products based on available literature.

Without this requested data significant benefit of the proposed product cannot be assessed.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor elaborated on bibliographical data on the pharmaceutical characteristics of the product and compatibility with different foods. The sponsor however did not present any data with the product in either preclinical models or patients affected by the condition. The COMP considered that in the absence of data with the product, the criteria for designation cannot be justified

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2015, prior to final opinion.

2.1.9 Product for treatment of ornithine transcarbamylase deficiency - EMA/OD/226/14

[COMP coordinators: L. Greene/ V. Tillmann]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Ornithine transcarbamylase deficiency, the sponsor was asked to further elaborate on:

  - the pharmaceutical characteristics of the product, in particular pharmacokinetics, stability, and compatibility with food or beverages;
  - the excipients and the potential safety concerns for infants and children in this regard.

In the absence of data, medical plausibility of the proposed product, in particular with regards to the proposed formulation, cannot be assessed.

- Significant benefit

The arguments on significant benefit were based on a major contribution to patient care and the potential improved safety in the condition.

The sponsor was requested to further discuss the argument on a major contribution to patient care based on results from any available study or clinical experience with the proposed product documenting patients' experience, e.g. in the context of a validated questionnaire, to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor was also requested to elaborate in more detail on the claimed safety concerns with authorised medicinal products based on available literature.

Without this requested data significant benefit of the proposed product cannot be assessed.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor elaborated on bibliographical data on the pharmaceutical characteristics of the product and compatibility with different foods. The sponsor however did not present any data with the product in either preclinical models or patients affected by the condition. The COMP considered that in the absence of data with the product, the criteria for designation cannot be justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2015, prior to final opinion.

2.1.10 Product for treatment of argininosuccinate synthetase deficiency - EMA/OD/229/14
[COMP coordinators: L. Greene/ V. Tillmann]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

The COMP considered that the condition originally proposed by the sponsor should be renamed as “cittrulinaemia type 1” based on the currently used nomenclature in the scientific community.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of cittrulinaemia type 1, the sponsor was asked to further elaborate on:

  - the pharmaceutical characteristics of the product, in particular pharmacokinetics, stability, and compatibility with food or beverages;
  - the excipients and the potential safety concerns for infants and children in this regard.

In the absence of data, medical plausibility of the proposed product, in particular with regards to the proposed formulation, cannot be assessed.

- Significant benefit

The arguments on significant benefit were based on a major contribution to patient care and the potential improved safety in the condition.

The sponsor was requested to further discuss the argument on a major contribution to patient care based on results from any available study or clinical experience with the proposed product documenting patients’ experience, e.g. in the context of a validated questionnaire, to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor was also requested to elaborate in more detail on the claimed safety concerns with authorised medicinal products based on available literature.

Without this requested data, significant benefit of the proposed product cannot be assessed.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor elaborated on bibliographical data on the pharmaceutical characteristics of the product and compatibility with different foods. The sponsor however did not present any data with the product in

either preclinical models or patients affected by the condition. The COMP considered that in the absence of data with the product, the criteria for designation cannot be justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2015, prior to final opinion.

2.1.11 Fibrinogen-coated albumin spheres for treatment of Ebola viral infection, Fibreu Limited - EMA/OD/250/14
[COMP coordinator: J. Torrent-Farnell]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Ebola *viral infection*, the sponsor was asked to further elaborate on:

- the relevance of the irradiation model to the intended clinical use of the product in Ebola virus disease, including, among others, discussion on the role and type of cytokine storm in irradiation and in Ebola infection;
- the relevance of the irradiation model vis a vis currently available models to study the clinical manifestations of Ebola virus disease;
- the effects of the product in non-thrombocytopenic conditions, since thrombocytopenia is not necessarily associated with the haemorrhagic manifestations of Ebola;
- the rationale of the proposed product versus other types of currently available fibrinogen formulations.

In the written response, the sponsor discussed the pathogenetic events of the model presented to support the medical plausibility in the proposed indication. The sponsor highlighted similarities in the cytokine storm and cellular damage in both settings, and while acknowledging the obvious difference of the causative agents involved, argued that in both cases non-specific mechanisms are ultimately responsible for cellular damage and vascular leakage.

The COMP noted that there is uncertainty with regards to the best model for evaluating the efficacy of supportive treatments such as the one proposed in Ebola virus disease. It was considered that preclinical models of Ebola infection are available, but this is far less established for treatments targeting the consequences of the infection, also taking into account the different pathogenetic events triggered by Ebola. In this view a non-specific model was seen not less relevant than a model of the specific infection since the events of interest are not strictly infection-specific.

Following review of the application by the Committee, it was agreed to rename the indication to Ebola virus disease.

The Committee agreed that the condition, Ebola virus disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing fibrinogen-coated albumin spheres was considered justified based on increased survival in preclinical models characterised by activation of cytokine storm and vascular leakage, similar to what happens in Ebola virus disease.

The condition is life-threatening due to severe, fluid-depleting diarrhoea leading to hypotension and shock, with diffuse haemorrhage in the severe forms of the disease.

The condition was estimated to be affecting less than 0.01 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for fibrinogen-coated albumin spheres for treatment Ebola virus disease, was adopted by consensus.

2.1.12 Product for treatment of Sjogren's syndrome - EMA/OD/235/14

[COMP coordinator: Z. Batova]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Number of people affected

The sponsor has based their calculation on patients who present with keratoconjunctivitis sicca or keratitis and keratoconjunctivitis. This represents a level of severity of the condition and therefore a subset which is not adequate for the purpose of calculating the prevalence. The sponsor was requested to calculate the prevalence for the whole population affected by Sjögren's syndrome which has been reported to be of the order of 6 in 1000.

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was asked to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved efficacy in the condition. This would represent a clinically relevant advantage.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preclinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor further elaborated on the prevalence of sjogren syndrome and discussed the heterogeneity of the different figures reported in the literature. Significant benefit was argued on the basis of improved safety and tolerability versus currently authorised products.

The COMP considered that the prevalence of the condition has been reported in excess of the provision threshold for orphan designation, while the significant benefit argument was also not based on data.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 January 2015, prior to final opinion.

2.1.13 Product for treatment of Ebola virus disease - EMA/OD/272/14
[COMP coordinator: N. Sypsas]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of Ebola virus disease, the sponsor was asked to further elaborate on:

  - the relevance of the in vitro data showing the effect of the product on viruses other than Ebola (and other than filoviruses) to the treatment of Ebola virus disease;
  - the methodology and results of the experiment showing serum levels of the product vs. time, and their relevance to the intended use in Ebola virus disease.

In the written response, and during an oral explanation before the Committee on 7 January 2015, the sponsor elaborated on the relevance of the in vitro studies on other viruses based on commonalities in the evasion of human innate immune system and also discussed the pharmacokinetics of the product based on results from studies in healthy volunteers. The COMP considered that the absence of data in relevant models of the condition would not allow the justification of medical plausibility criterion.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 January 2015, prior to final opinion.

2.1.14 Product for treatment of mantle cell lymphoma - EMA/OD/220/14
[COMP coordinator: K. Kubáčková]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of mantle cell lymphoma, the sponsor was asked to further elaborate on the relevance of the preclinical model used for the treatment of mantle cell lymphoma, in particular with regards to the preventive settings used, and the interpretation of the results obtained in the experiments.

- Number of people affected

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was asked to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was required perform a sensitivity analysis of the reported calculations.

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved efficacy in the condition.

The sponsor was asked to detail the results of any preclinical or preliminary clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of the target condition.

In the written response, and during an oral explanation before the Committee on 8 January 2015, the sponsor further elaborated on the issues raised.

With regards to the preventive settings used for the justification of significant benefit, the sponsor argued that the xenochimeric model used necessitated the use of such settings.

With regards to prevalence, the estimate was revised upwards to 1/10,000 based on the incidence referred to in the ESMO treatment guidelines multiplied by a factor of 5 to reflect the duration of the condition. Finally with regards to the significant benefit, the sponsor stated that it was now targeting a maintenance therapeutic indication, after taking into consideration the preventive effects observed. The sponsor also discussed literature studies with other similar products that would support additional effects when combined with other existing treatments.

The COMP considered that the justification of medical plausibility could not be accepted in the absence of data in the either relevant models of the condition as applied for designation or in preliminary clinical settings, in line with the guideline on the format and content of applications (ENTR/6283/00 rev 04). The COMP also considered that the bridging to other products for the justification of medical plausibility would be difficult to consider to reach a conclusion on the specific product under review.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 09 January 2015, prior to final opinion.

2.1.15 Product for treatment of non-infectious uveitis - EMA/OD/236/14

[COMP coordinator: K. Westermark]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 5 January 2015, prior to responding to the list of issues.

2.1.16 Product for treatment of Creutzfeldt-Jacob Disease- EMA/OD/221/14

[COMP coordinator: S. Thorsteinsson]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Creuztfeldt-Jacob Disease, the sponsor was asked to further elaborate on the results obtained in the reported clinical studies, and document any beneficial effect of treatment in relevant endpoints in patients affected by the condition.

In the written response, and during an oral explanation before the Committee on 8 January 2015, the sponsor further elaborated on the available clinical studies, and stressed the difference in the included populations between studies. In particular, the inclusion of patients with very advanced disease was specifically mentioned for the studies that did not confirm the anticipated effect. The COMP considered

that in the absence of clear beneficial effects in either relevant models or patients affected by the condition, the justification of the criteria for designation was not met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 January 2015, prior to final opinion.

2.1.17 Product for treatment of glioma - EMA/OD/234/14

[COMP coordinator: A. Lhoir]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to treat

To establish correctly if there exists a scientific rationale for the development of the product for treatment of glioma, the sponsor was asked to further elaborate on:

  - the relevance of the results obtained in glioblastoma cell lines to the intended clinical use of the product;
  - the correlation between the concentrations in vitro and the potential doses that could have an effect in the clinical setting.

The sponsor was also invited to submit any other available preclinical and/or clinical data supporting the medical plausibility. In the absence of new data the medical plausibility cannot be considered acceptable based on the data presented up to date.

- Significant benefit

In order to justify the significant benefit the sponsor was requested to further elaborate on how the methodology and the results of the clinical case presented would support a clinical advantage of using the proposed product in combination with the current standard of care.

The sponsor was also invited to submit any other available preclinical and/or clinical data supporting the significant benefit. In the absence of new data the significant benefit cannot be considered acceptable based on the data presented up to date.

In the written response, and during an oral explanation before the Committee on 8 January 2015, the sponsor further discussed preclinical data from the literature, and presented two case-studies in preliminary clinical settings in patients affected by the condition. It was argued that the available in vitro data supported exertion of cytotoxicity in glioma cell lines, while the in vivo data supported the potential of increasing the effect of alkylating agents and the inhibiting micrometastasis. The sponsor also presented two clinical cases in patients affected by the proposed condition who were treated in combination with other products including temozolomide. The COMP considered that the preclinical data presented did not document direct clinically relevant outcomes, while the uncontrolled nature of the clinical cases as well as the concomitant use of other products would not allow the criteria for designation to be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 January 2015, prior to final opinion.

2.1.18 3-[2-(4-Carbamimidoyl-phenylcarbamoyl)-5-methoxy-4-vinyl-phenyl]-6-(cyclopropylmethyl-carbamoyl)-pyridine-2-carboxylic acid for treatment of angioedema, BioCryst UK Ltd. - EMA/OD/170/14
[COMP coordinator: M. Možina]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

The condition should be justified as a distinct medical entity or a valid subset. The COMP noted that a new classification of angioedema identifies hereditary angioedema and acquired angioedema. The COMP considered that this condition should fall under hereditary angioedema (Cicardi *et al* Allergy 2014; 69: 602–616).

- Number of people affected

The sponsorwas invited to recalculate the prevalence for hereditary angioedema.

For the calculation and presentation of the prevalence estimate the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

The sponsor was asked to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor was asked to describe and justify the methodology used for the prevalence calculation.

- Significant benefit

The sponsor was proposing that significant benefit is based on an alternative mode of action which would offer a clinically relevant advantage over current approved treatments in Europe.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the Phase II study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 8 January 2015, the sponsor accepted to change the proposed condition to hereditary angioedema and recalculated the prevalence accordingly. With regards to the issue of significant benefit the sponsor argued that this stems from a different mode of action to currently authorised therapies. It was argued that the available clinical data with the product supported its use in the context of secondary prevention that would reduce the need for infusions of C1 inhibitor. They also highlighted the major contribution to patient care in the treatment of these patients using an oral administration of their product.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to hereditary angioedema.

The Committee agreed that the condition, hereditary angioedema, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 3-[2-(4-carbamimidoyl-phenylcarbamoyl)-5-methoxy-4-vinyl-phenyl]-6-(cyclopropylmethyl-carbamoyl)-pyridine-2-carboxylic acid was considered justified based on preliminary clinical studies showing reduction of weekly angioedema attack rate in treated patients affected by the condition.

The condition is life-threatening and chronically debilitating due to recurrent attacks of oedema in various parts of the body that may cause airway obstruction leading to asphyxia.

The condition was estimated to be affecting approximately 0.15 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 3-[2-(4-carbamimidoyl-phenylcarbamoyl)-5-methoxy-4-vinyl-phenyl]-6-(cyclopropylmethyl-carbamoyl)-pyridine-2-carboxylic acid may be of significant benefit to those affected by the condition. This was considered on the basis of an oral formulation that would compare favourably with the currently available products which are administered via the intravenous route. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for 33-[2-(4-carbamimidoyl-phenylcarbamoyl)-5-methoxy-4-vinyl-phenyl]-6-(cyclopropylmethyl-carbamoyl)-pyridine-2-carboxylic acid for treatment of hereditary angioedema, was adopted by consensus.

2.1.19 Nitroglycerin for treatment of systemic sclerosis, Covis Pharma S.à.r.l. - EMA/OD/225/14
[COMP coordinator: G. O'Dea]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Intention to diagnose, prevent or treat

In order to justify the intention to treat the proposed condition the sponsor was invited to further discuss:

  - the reasons to restrict the use of the proposed product to systemic sclerosis, taking into account that Raynaud phenomenon occurs as secondary to a number of different conditions, in addition to the primary form;
  - the study from Chung *et al* (2009), showing greater efficacy of nitroglycerin in primary Raynaud phenomenon than in Raynaud's secondary to systemic sclerosis.

- Prevalence

The sponsor was asked to further explain how they calculated prevalence rates for systemic sclerosis.

For the calculation and presentation of the prevalence data the sponsor was advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation" document available on the EMA website.

- Significant benefit

The sponsor was invited to support the claims of significant benefit of the proposed product over bosentan with any available data.

In the written response, and during an oral explanation before the Committee on 8 January 2015, the sponsor clarified the relevance of Raynaud's phenomenon for the proposed condition, stressing that Raynaud's occurs in 95% of cases of systemic sclerosis and leads to important clinical consequences such as development of digital ulcers. With regards to the grounds for significant benefit the sponsor

discussed the available literature of clinical studies supporting a better efficacy of nitroglycerin compared to bosentan in particular with regards to Raynaud phenomenon scores.

The Committee agreed that the condition, systemic sclerosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing nitroglycerin was considered justified based on clinical data showing improvement of Raynaud's phenomenon in systemic sclerosis with the proposed product.

The condition is chronically debilitating and life-threatening due to the deposition of collagen in the skin and in internal organs such as kidneys, heart, lungs and gastrointestinal tract, leading to severe complications such as pulmonary hypertension, progressive dysphagia, sclerodermal renal crisis and cardiac failure.

The condition was estimated to be affecting less than 3.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing nitroglycerin may be of significant benefit to those affected by the condition. There are no treatments authorised for systemic sclerosis that could stop the build-up of collagen. Bosentan was authorised in the EU specifically to treat patients with systemic sclerosis who have pulmonary arterial hypertension or digital ulcers. The sponsor has provided literature data from clinical trials that demonstrate a more favourable outcome on Raynaud phenomenon scores in systemic sclerosis than bosentan, currently authorized for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by systemic sclerosis.

A positive opinion for nitroglycerin for treatment of systemic sclerosis, was adopted by consensus.

2.1.20 Product for treatment of diastolic heart failure caused by hypertrophic cardiomyopathy - EMA/OD/153/14
[COMP coordinator: J. Torrent-Farnell]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 5 January 2015, prior to responding to the list of issues.

2.1.21 Sevuparin sodium for treatment of sickle cell disease, Dilaforette AB - EMA/OD/210/14
[COMP coordinator: A. Moraiti]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the following issues:

- Significant benefit

The arguments on significant benefit were based on the new mechanism of action and the potential improved safety in the condition. It was noted that extrapolation from preclinical or early clinical studies could not predict the safety of a product in its clinical setting, thus more relevant data was mandatory to justify safety arguments in most cases.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results of any studies with the product in the condition, in order to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 9 January 2015, the sponsor further discussed the issue of significant benefit. As regards to the argument of improved safety the sponsor elaborated on the preliminary clinical data available, while with regards to a potentially improved efficacy, the sponsor stressed that the new mechanism of action would probably translate into treatment of acute vaso-occlusive crisis.

The Committee agreed that the condition, sickle cell disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sevuparin sodium was considered justified based on preclinical data showing improvement in vascular flow in a model of vaso-occlusive crisis.

The condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections, and life-threatening with reduced survival.

The condition was estimated to be affecting approximately 2.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sevuparin sodium may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that support the potential of the product in the treatment of acute vaso-occlusive crises. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for sevuparin sodium for treatment of sickle cell disease, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1 2'-*O*-methyl phosphorothioate RNA oligonucleotide, 5'-m^5CUGm^5CUGm^5CUGm^5CUGm^5CUGm^5CUGm^5CUG-3' for treatment of Huntington's disease, Prosensa Therapeutics B.V. - EMA/OD/192/14

[COMP coordinator: A. Magrelli]

The Committee agreed that the condition, Huntington's disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2'-*O*-methyl phosphorothioate RNA oligonucleotide, 5'-m^5CUGm^5CUGm^5CUGm^5CUGm^5CUGm^5CUGm^5CUG-3' was considered justified based on pre-clinical data in a valid model of the condition showing improved movement and coordination following treatment.

The condition is chronically debilitating due to severe behavioural and cognitive disturbances, progressive motor dysfunction and potentially fatal complications.

The condition was estimated to be affecting approximately 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2'-*O*-methyl phosphorothioate RNA oligonucleotide, 5'-m^5CUGm^5CUGm^5CUGm^5CUGm^5CUGm^5CUGm^5CUG-3' may be of significant benefit to those affected by the condition/to the population at risk of developing the condition. This is based on the proposed mechanism of action that targets the expression of mutated Huntington. The COMP considered that this may translate into effects in broader aspects of the condition compared to currently available authorised treatments. The sponsor has provided pre-clinical data that support this assumption. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2'-*O*-methyl phosphorothioate RNA oligonucleotide, 5'-m^5CUGm^5CUGm^5CUGm^5CUGm^5CUGm^5CUGm^5CUG-3' for treatment of Huntington's disease, was adopted by consensus.

2.2.2 Product for treatment of Alport syndrome - EMA/OD/238/14

[COMP coordinator: A. Corrêa Nunes]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to respond to the list of issues in writing before the February Committee meeting.

2.2.3 505 amino acid protein, corresponding to amino acids 2-506 of the wild type human histidyl-tRNA Synthetase for treatment of facioscapulohumeral muscular dystrophy, Voisin Consulting S.A.R.L. - EMA/OD/268/14

[COMP coordinator: A. Corrêa Nunes]

The Committee agreed that the condition, facioscapulohumeral muscular dystrophy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 505 amino acid protein, corresponding to amino acids 2-506 of the wild type human histidyl-tRNA synthetase was considered justified based on data from preclinical models demonstrating that the product reduced skeletal muscle degeneration, necrosis, and inflammation.

The condition is chronically debilitating due to progressive severe weakness of skeletal muscles, leading to impaired mobility, chronic fatigue and pain, visual loss and hearing impairment. Patients with infantile onset disease have a reduced life-expectancy, with death usually occurring in the 3rd decade of life.

The condition was estimated to be affecting not more than 1 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for 505 amino acid protein, corresponding to amino acids 2-506 of the wild type human histidyl-tRNA synthetase for treatment of facioscapulohumeral muscular dystrophy, was adopted by consensus.

2.2.4 5-hydroxymethyl-2-furfural for treatment of sickle cell disease, Baxter Innovations GmbH - EMA/OD/249/14
[COMP coordinator: L. Gramstad]

The Committee agreed that the condition, sickle cell disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 5-hydroxymethyl-2-furfural was considered justified based on preclinical data showing increased survival under hypoxic conditions with the proposed product.

The condition is chronically debilitating in particular due to vaso-occlusive crises, haemolytic anaemia, acute chest syndrome, chronic kidney disease, pulmonary hypertension and susceptibility to infections, and life-threatening with reduced survival.

The condition was estimated to be affecting approximately 2.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 5-hydroxymethyl-2-furfural may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data supporting the potential use of the proposed product in combination with currently authorised treatments for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by sickle cell disease.

A positive opinion for 5-hydroxymethyl-2-furfural for treatment of sickle cell disease was adopted by consensus.

2.2.5 Product for treatment of Netherton syndrome - EMA/OD/264/14
[COMP coordinator: A. Andrić]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.6 Product for treatment of idiopathic noncirrhotic portal hypertension - EMA/OD/269/14
[COMP coordinator: A. Corrêa Nunes]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.7 Allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus for treatment of cytomegalovirus (CMV) infections in patients following allogeneic stem cell transplantations, Miltenyi Biotec GmbH - EMA/OD/246/14
[COMP coordinator: B. Dembowska-Bagińska]

The Committee agreed that the condition, originally proposed by the sponsor should be renamed as “treatment of cytomegalovirus infection following haematopoietic stem cell transplantation”

(hereinafter referred to as “the condition”), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus was considered justified based on clinical reports showing reduction of viral load and favourable clinical outcome with the proposed product.

The condition is life-threatening and chronically debilitating due to viral invasion of different organs and to indirect effects on the immune system that increase the risk of other infections and promote acute graft rejection.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus may be of significant benefit to those affected by the condition. The sponsor provided data on clinical cases showing clearance of viral loads and improved survival in patients refractory to previous antiviral treatment. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by cytomegalovirus infection following haematopoietic stem-cell transplantation.

A positive opinion for allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus for treatment of cytomegalovirus infection in patients following haematopoietic stem-cell transplantation was adopted by consensus.

2.2.8 Allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus

for treatment of Epstein-Barr Virus infections in patients following allogeneic stem cell transplantations, Miltenyi Biotec GmbH - EMA/OD/247/14
[COMP coordinator: B. Dembowska-Bagińska]

The Committee agreed that the condition, originally proposed by the sponsor should be renamed as “treatment of Epstein-Barr virus infection following haematopoietic stem cell transplantation” (hereinafter referred to as “the condition”), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus was considered justified based on clinical reports showing reduction of viral load and favourable clinical outcome with the proposed product.

The condition is life-threatening and chronically debilitating due to the development of enteritis with multiple ulcers, hepatitis, encephalitis and extensive lymphadenopathy; EBV infections do progress to post-transplant lymphoproliferative disease in about 10% of cases.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

The Committee considered the information provided by the applicants on the significant benefit of the medicinal product containing allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus over existing methods of treatment. The sponsor provided studies on clinical cases showing clearance of viral loads and improved survival in patients refractory to previous antiviral treatment. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by Epstein-Barr virus infection following haematopoietic stem cell transplantation.

A positive opinion for allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus for treatment of Epstein-Barr virus infection following haematopoietic stem cell transplantation was adopted by consensus.

Post-meeting note:

Clarification was obtained after the meeting that none of the alternative methods of treatment were authorised. The summary assessment report will be amended accordingly and tabled for re-adoption at the February meeting.

2.2.9 Allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus for treatment of adenovirus infections in patients following allogeneic stem cell transplantations, Miltenyi Biotec GmbH - EMA/OD/245/14

[COMP coordinator: B. Dembowska-Bagińska]

The Committee agreed that the condition, originally proposed by the sponsor should be renamed as “treatment of adenovirus infection following haematopoietic stem cell transplantation” (hereinafter referred to as “the condition”), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus was considered justified based on clinical reports showing reduction of viral load and favourable clinical outcome with the proposed product.

The condition is life-threatening and chronically debilitating due to interstitial pneumonitis, hepatitis, haemorrhagic cystitis or nephritis, haemorrhagic colitis, central nervous system disease and disseminated disease. Mortality rate is up to 67%.

The condition was estimated to be affecting less than 0.1 in 10,000 persons in the European Union, at the time the application was made.

The Committee considered the information provided by the applicants on the significant benefit of the medicinal product containing allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus over existing methods of treatment. The sponsor provided studies on clinical cases showing clearance of viral loads and improved survival in patients refractory to previous antiviral treatment. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by adenovirus infection following haematopoietic stem cell transplantations.

A positive opinion for allogeneic CD4+ and CD8+ T lymphocytes ex vivo incubated with synthetic peptides of the viral antigens of cytomegalovirus, adenovirus and Epstein-Barr virus for treatment of adenovirus infection following haematopoietic stem cell transplantation was adopted by consensus.

Post-meeting note:

Clarification was obtained after the meeting that none of the alternative methods of treatment were authorised. The summary assessment report will be amended accordingly and tabled for re-adoption at the February meeting.

2.2.10 Product for treatment of biliary tract cancer - EMA/OD/252/14
[COMP coordinator: A. Magrelli]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.11 Alvocidib for treatment of acute myeloid leukemia, Theorem Clinical Research GmbH - EMA/OD/240/14
[COMP coordinator: B. Dembowska-Bagińska]

The Committee agreed that the condition, acute myeloid leukaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing alvocidib was considered justified based on preclinical and clinical data showing antitumor efficacy.

The condition is life-threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%.

The condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing alvocidib may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable responses when the product was used in combination with the currently authorised treatment regimen for the proposed condition including in patients relapsing after previous treatment. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by acute myeloid leukaemia.

A positive opinion for alvocidib for treatment of acute myeloid leukaemia was adopted by consensus.

2.2.12 Product for treatment of eosinophilic oesophagitis - EMA/OD/243/14
[COMP coordinator: A. Corrêa Nunes]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.13 Product for treatment of Huntington's disease - EMA/OD/255/14
[COMP coordinator: A. Andrić]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.14 Product for treatment of creatine transporter deficiency - EMA/OD/239/14
[COMP coordinator: A. Moraiti]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.15 Product for treatment of graft versus host disease - EMA/OD/267/14
[COMP coordinator: F. Naumann-Winter]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.16 ***Lactobacillus reuteri*** for prevention of necrotising enterocolitis, Infant Bacterial Therapeutics AB - EMA/OD/237/14
[COMP coordinator: S. Thorsteinsson]

The Committee agreed that the condition, necrotising enterocolitis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing *Lactobacillus reuteri* was considered justified based on bibliographic studies showing reduction in the incidence of necrotizing enterocolitis in preterm infants that have been administered with *Lactobacillus reuteri*.

The condition is chronically debilitating due to development of short-bowel syndrome, malnutrition, and growth delay, and life-threatening due to bowel perforation, peritonitis, sepsis and mortality reported as high as in 50% of the cases.

The population of patients eligible for prevention of the condition was estimated to be approximately 4.5 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of prevention that has been authorised in the European Union for patients affected by the condition.

A positive opinion for *Lactobacillus reuteri* for prevention of necrotising enterocolitis was adopted by consensus.

2.2.17 Product for treatment of Wilson disease - EMA/OD/241/14
[COMP coordinator: K. Westermark]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.18 Mazindol for treatment of narcolepsy, HAC Pharma - EMA/OD/254/14
[COMP coordinator: A. Andrić]

The Committee agreed that the condition, narcolepsy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing mazindol was considered justified based on clinical observations that report improvement in excessive sleepiness and cataplexy in treated patients affected by the condition.

Condition is chronically debilitating in particular due to excessive daytime sleepiness and cataplexy episodes, as well as life-threatening with a 1.5-fold excess mortality in narcolepsy patients relative to those without narcolepsy.

The condition was estimated to be affecting less than 4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mazindol may be of significant benefit to those affected by the condition. The sponsor has provided clinical observations showing responses in patients that were resistant to treatment with available products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for mazindol for treatment of narcolepsy was adopted by consensus.

2.2.19 Myriocin for treatment of retinitis pigmentosa, Nanovector s.r.l. - EMA/OD/271/14
[COMP coordinator: A. Magrelli]

The Committee agreed that the condition, retinitis pigmentosa, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing myriocin was considered justified based on a valid pre-clinical model of the condition which showed a preservation of the cones in the retina and therefore vision.

The condition is chronically debilitating due to the development of nyctalopia and tunnel vision that progresses to total blindness.

The condition was estimated to be affecting approximately 2.4 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for myriocin for treatment of retinitis pigmentosa was adopted by consensus.

2.2.20 N-(3-(4-(3-(diisobutylamino)propyl)piperazin-1-yl)propyl)-1H-benzo[d]imidazol-2-amine disulphate salt for treatment of progressive supranuclear palsy, AlzProtect sas - EMA/OD/261/14
[COMP coordinator: J. Torrent-Farnell]

The Committee agreed that the condition, progressive supranuclear palsy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing N-(3-(4-(3-(diisobutylamino)propyl)piperazin-1-yl)propyl)-1H-benzo[d]imidazol-2-amine disulphate salt was considered justified based on pre-clinical data using a valid model of the condition where there was an improvement in memory deficits and a significant reduction in incorrect forelimb placement.

The condition is chronically debilitating due to progressive neurological impairment including development of parkinsonism, inability to walk, progressive paralysis and cognitive deterioration. The condition is life-threatening, leading to premature death.

The condition was estimated to be affecting approximately 1.4 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for N-(3-(4-(3-(diisobutylamino)propyl)piperazin-1-yl)propyl)-1H-benzo[d]imidazol-2-amine disulphate salt for treatment of progressive supranuclear palsy was adopted by consensus.

2.2.21 Product for treatment of pancreatic cancer - EMA/OD/242/14
[COMP coordinator: B. Bloechl-Daum]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.22 Product for treatment of uremic pruritus - EMA/OD/265/14
[COMP coordinator: J. Torrent-Farnell]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.23 Olaratumab for treatment of soft tissue sarcoma, Eli Lilly Nederland B.V. - EMA/OD/266/14
[COMP coordinator: A. Andrić]

The Committee agreed that the condition, soft tissue sarcoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing olaratumab was considered justified based on preliminary clinical data in patients affected by the condition, where treatment with the proposed product in combination with doxorubicin improved a clinically relevant outcome.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

The condition was estimated to be affecting not more than 3 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal

product containing olaratumab may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing improvement in a clinically relevant outcome in combination with doxorubicin. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for olaratumab for treatment of soft tissue sarcoma was adopted by consensus.

2.2.24 Product for treatment of amyotrophic lateral sclerosis - EMA/OD/262/14
[COMP coordinator: E. Kaisi]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.25 Product for prevention of bronchopulmonary dysplasia - EMA/OD/270/14
[COMP coordinator: K. Westermark]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.26 Recombinant human glutamate oxaloacetate transaminase 1 for treatment of glioma, Impasara Ltd - EMA/OD/251/14
[COMP coordinator: D. O'Connor]

The Committee agreed that the condition, glioma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant human glutamate oxaloacetate transaminase 1 was considered justified based on preclinical data showing an effect of the proposed product on tumour size and on survival.

The condition is chronically debilitating due to symptoms caused by compression by the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. The condition is life-threatening, with poor 5-year survival of less than 5% for glioblastoma multiforme patients.

The condition was estimated to be affecting less than 2.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human glutamate oxaloacetate transaminase 1 may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing a beneficial effect on survival when the proposed product was added to temozolomide, currently authorized for the treatment of glioma. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by glioma.

A positive opinion for recombinant human glutamate oxaloacetate transaminase 1 for treatment of glioma was adopted by consensus.

2.2.27 Product for treatment of Smith-Magenis syndrome - EMA/OD/260/14
[COMP coordinators: G. Capovilla/ I. Bradinova]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.28 Product for treatment of fragile X syndrome - EMA/OD/253/14
[COMP coordinator: I. Bradinova]

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

2.2.29 Ulocuplumab for treatment of acute myeloid leukaemia, Bristol-Myers Squibb Pharma EEIG - EMA/OD/258/14
[COMP coordinator: B. Dembowska-Bagińska]

The Committee agreed that the condition, acute myeloid leukaemia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing ulocuplumab was considered justified based on preliminary clinical data in patients with relapsed or refractory acute myeloid leukaemia who responded to treatment.

The condition is life threatening due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections.

The condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ulocuplumab may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate an improved overall remission rate in relapsed/refractory AML patients compared to historical controls. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ulocuplumab for treatment of acute myeloid leukaemia was adopted by consensus.

2.3. Appeal procedure

None.

2.4. Evaluation on-going

The Committee noted that evaluation was on-going for thirty six applications for orphan designation.

2.5. Validation on-going

The Committee was informed that validation was on-going for forty three applications for orphan designation.

3. Requests for protocol assistance

3.1 For treatment of African trypanosomiasis [Coordinator: B. Bloechl-Daum]

The Committee was briefed on the significant benefit issues. The COMP answer on the significant benefit issues was adopted.

3.2 For treatment of Stargardt's disease. [Co-ordinator: K. Westermark]

The Committee was briefed on the significant benefit issues. The COMP answer on the significant benefit issues was adopted.

4. Overview of applications

4.1 Update on applications for orphan medicinal product designation submitted/expected

COMP co-ordinators were appointed for 1 application submitted and 19 upcoming applications.

4.2 Update on orphan applications for Marketing Authorisation

An updated overview of orphan applications for Marketing Authorisation was circulated.

5. Review of orphan designation for orphan medicinal products for Marketing Authorisation

5.1. Orphan designated products for which CHMP opinions have been adopted

5.1.1 Holoclar (Ex vivo expanded autologous human corneal epithelium containing stem cells) for treatment of corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns; Chiesi Farmaceutici S.p.A.
(EU/3/08/579) [COMP Co-ordinator: V. Stoyanova]

The COMP noted the CHMP opinion on MA adopted 15-18 December 2014 meeting.

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to elaborate on the following issues:

- Significant benefit

The sponsor is requested to present the established methods of treatment (including keratoplasty) for the target population and position their product in the treatment of these patients. A comparative discussion based on data regarding the results of the proposed product versus the results with the established methods is expected.

In its written response, the sponsor discussed different surgical techniques used in the treatment of the condition. With regards to limbal transplantation procedures, these were presented with reference to the donor used (fellow eye for autologous procedures, living relative, living not relative and cadaveric), and the transplanted tissue (conjunctival limbal or keratolimbal grafts). In addition the sponsor also discussed oral epithelial cells as source for transplantation and penetrating keratoplasty.

In this context, the sponsor included several arguments for the significant benefit issue as described below:

- With regards to other autologous limbal stem cell techniques, the sponsor argued that these may not be performed in the presence of bilateral lesions in contrast to the proposed therapy which may be applied where minimal source tissue is intact (1-2 mm^2).
- With regards to allogeneic procedures (including living and non-living donors), the lack of dependency of the proposed treatment on immunosuppression was also discussed.
- With regards to other surgical procedures such as oral epithelial transplantation, the sponsor discussed the lack of long-term efficacy data.
- Finally, the sponsor also pointed out that in cases of deep damage the use of Holoclar may increase, the likelihood for a successful subsequent keratoplasty.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be less than 0.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to visual impairment.

Although satisfactory methods of treatment of the condition exist in the European Union, the assumption that Holoclar may be of potential significant benefit to those affected by the orphan condition still holds. Significant benefit was considered with reference to existing surgical procedures, on the basis of the lack of dependence on immune suppression, the possibility to administer Holoclar in patients with minimal residual limbal stem cells and the possibility to use in addition to existing surgical procedures. The COMP considered that this constitutes a clinically relevant advantage.

The proposed therapeutic indication “corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns” falls entirely within the scope of the orphan indication of the designated orphan medicinal product.

An opinion not recommending the removal of Holoclar, ex vivo expanded autologous human corneal epithelium containing stem cells, EU/3/08/579, from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion was adopted for publication on the EMA website.

5.1.2 Quinsair (Levofloxacin hemihydrate) for treatment of cystic fibrosis; Aptalis Pharma SAS (EU/3/08/566) [COMP Co-ordinator: J. Eggenhofer]
The COMP noted the CHMP opinion on MA adopted 15-18 December 2014 meeting.

The COMP adopted a list of issues to be sent to the sponsor. The sponsor will be invited to an oral explanation before the Committee at the February meeting.

5.2. Orphan designated products for discussion prior to adoption of CHMP opinion

5.2.1 Ruxolitinib for treatment of polycythaemia vera; Novartis Europharm Limited (EU/3/14/1244)

5.3. On-going procedures

5.3.1 Blinatumomab for treatment of acute lymphoblastic leukaemia; Amgen Europe B.V. (EU/3/09/650)

5.3.2 Mifepristone for treatment of hypercortisolism (Cushing's syndrome) of endogenous origin; FGK Representative Service GmbH (EU/3/11/925)

5.3.3 Isavuconazonium sulfate; Basilea Medical Ltd:

a) treatment of invasive aspergillosis (EU/3/14/1284)

b) treatment of mucormycosis (EU/3/14/1276)

5.3.4 Cysteamine hydrochloride for treatment of cystinosis; Orphan Europe S.A.R.L. (EU/3/08/578)

5.3.5 Autologous tumour-derived immunoglobulin idiotype coupled to keyhole limpet haemocyanin for treatment of follicular lymphoma; Biovest Europe Ltd (EU/3/06/394)

5.3.6 Efmoroctocog alfa for treatment of haemophilia A; Biogen Idec Ltd (EU/3/10/783)

5.3.7 Panobinostat for treatment of multiple myeloma; Novartis Europharm Limited (EU/3/12/1063)

5.3.8 Human heterologous liver cells (for infusion); Cytonet GmbH&Co KG

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/821)

b) treatment of ornithine-transcarbamylase deficiency (EU/3/07/470)

c) treatment of citrullinaemia type 1 (EU/3/10/818)

d) treatment of hyperargininaemia (EU/3/10/819)

e) treatment of argininosuccinic aciduria (EU/3/10/820)

5.3.9 Tasimelteon for treatment of non-24-hour sleep-wake disorder in blind people with no light perception; Vanda Pharmaceuticals Limited (EU/3/10/84)

5.3.10 Tolvaptan for treatment of autosomal dominant polycystic kidney disease; Otsuka Pharmaceutical Europe Ltd (EU/3/13/1175)

5.3.11 Ketoconazole for treatment of Cushing's syndrome; Agenzia Industrie Difesa-Stabilimento Chimico Farmaceutico Militare (EU/3/12/1031)

5.3.12 Lenvatinib; Eisai Ltd

a) treatment of papillary thyroid cancer (EU/3/13/1121)

b) treatment of follicular thyroid cancer (EU/3/13/1119)

5.3.13 Recombinant human parathyroid hormone for treatment of hypoparathyroidism; NPS Pharma UK Ltd (EU/3/13/1210)

5.3.14 Susoctocog alfa for treatment of haemophilia A; Baxter AG (EU/3/10/784)

5.3.15 Glyceryl tri-(4-phenylbutyrate); Hyperion Therapeutics Limited:

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/733)

b) treatment of ornithine carbamoyltransferase deficiency (EU/3/10/734)

c) treatment of citrullinaemia type 1 (EU/3/10/735)

d) treatment of argininosuccinic aciduria (EU/3/10/736)

e) treatment of hyperargininaemia (EU/3/10/737)

f) treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) (EU/3/10/738)

g) treatment of citrullinaemia type 2 (EU/3/10/739)

5.3.16 Idebenone for treatment of Leber's hereditary optic neuropathy; Santhera Pharmaceuticals (Deutschland) GmbH (EU/3/07/434)

5.3.17 L-Asparaginase for treatment of acute lymphoblastic leukaemia; medac Gesellschaft fuer klinische Spezialpraeparate mbH (EU/3/04/258)

5.3.18 Asfotase alfa for treatment of hypophosphatasia; Alexion Europe SAS (EU/3/08/594)

5.3.19 Chimeric monoclonal antibody against GD2 for treatment of neuroblastoma; United Therapeutics Europe Ltd (EU/3/11/879)

5.3.20 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride for treatment of narcolepsy; Bioprojet (EU/3/07/459)

5.3.21 Herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes for adjunctive treatment in haematopoietic cell transplantation; MolMed S.p.A. (EU/3/03/168)

6. Procedural aspects

6.1 Significant Benefit Working group

6.2 ITF briefing meeting, January 2015

Call for expression of interest in participation to the task force briefing meeting (for COMP members).

7. Any other business

None.

Date of next COMP meeting: 10-12 February 2015

List of participants

including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 7-9 January 2015 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
André Lhoir	Member	Belgium	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Adriana Andrić	Member	Croatia	No interests declared	
Elena Kaisi	Member	Cyprus	No interests declared	
Katerina Kubacková	Member	Czech Republic	No restrictions applicable to this meeting	
Jens Ersbøll	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Judit Eggenhofer	Member	Hungary	No interests declared	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Dainis Krievins	Member	Latvia	No restrictions applicable to this meeting	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova	Member	Netherlands	No interests declared	
Lars Gramstad	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	Cannot participate in final deliberations and voting on 2.2.23	
Ana Corrêa Nunes	Member	Portugal	No interests declared	
Flavia Saleh	Member	Romania	No interests declared	
Zuzana Batova	Member	Slovak Republic	No interests declared	
Josep Torrent-Farnell	Member	Spain	No interests declared	
Kerstin Westermark	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No restrictions applicable to this meeting	
Birthe Byskov Holm	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Aikaterini Moraiti	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Giuseppe Capovilla	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Virginie Hivert	Observer	Eurordis	No restrictions applicable to this meeting	
Julian Isla	Observer	Eurordis	No interests declared	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the product(s) they have been invited to talk about.