23 April 2020
EMA/COMP/155348/2020
Human Medicines Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 17-19 March 2020

Chair: Violeta Stoyanova-Beninska – Vice-Chair: Armando Magrelli

17 March 2020, 08:45-18:50, remote virtual meeting

18 March 2020, 08:30-18:40, remote virtual meeting

19 March 2020, 08:30-13:55, remote virtual meeting

Disclaimers

Some of the information contained in this set of minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also vary during the course of the review. Additional details on some of these procedures will be published in the COMP meeting reports once the procedures are finalised.

Of note, this set of minutes is a working document primarily designed for COMP members and the work the Committee undertakes.

Further information with relevant explanatory notes can be found at the end of this document.

Note on access to documents

Some documents mentioned in the minutes cannot be released at present following a request for access to documents within the framework of Regulation (EC) No 1049/2001 as 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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

1. Introduction

1.1. Welcome and declarations of interest of members and experts

In accordance with the Agency's policy on handling of declarations of interests of scientific Committees' members and experts, based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants in upcoming discussions was identified.

Participants in this meeting were asked to declare any changes, omissions or errors to their declared interests and/or additional restrictions concerning the matters for discussion. No new or additional interests or restrictions were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure and as included in the list of participants. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 22 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

At the start of the meeting, in the light of the current crisis (Covid-19 pandemic) and as a temporary measure, the participants agreed by consensus to hold the meeting virtually and take decisions remotely.

1.2. Adoption of agenda

The agenda for 17-19 March 2020 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 18-20 February 2020 were adopted with no amendments and will be published on the EMA website.

Regarding COMP representatives at SAWP, COMP Members noted that further interactions are currently ongoing.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. DNA plasmid encoding IL-12 p35 and p40 genes - EMA/OD/0000019167

FGK Representative Service GmbH; Treatment of ovarian cancer

COMP Rapporteur: Frauke 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

The sponsor should re-calculate the prevalence estimate including also fallopian tube and primary peritoneal cancer.

In the re-calculation of the prevalence estimate the sponsor was also requested to use crude incidence rates of the condition, and to take into account the most recent available data for estimating survival rates.

In the written response, the sponsor assumed a duration of 5 years for ovarian cancer and used the formula incidence times duration for estimating prevalence. The crude incidence derived from ECIS (European Cancer Information System), and the number of cases of peritoneal cancer were derived from historical ECIS data derived from individual registries. Age-standardised incidence of fallopian tube cancers was based on the IARC (International Agency for Research on Cancer) database. It was considered that fallopian tube and peritoneal cancer comprise approximately 8% of the incidence of ovarian cancer.

In view that 5 year relative survival is still less than 50% of years for ovarian cancer (but long-term survivors exist), the duration of the condition of 5 years was considered by the COMP to be an acceptable approximation (likely to be conservative) to the mean survival needed for the formula P=I*D. The use of age-standardised incidence for fallopian cancer is likely an underestimate, but considering the small contribution to the overall results, this was accepted. The conclusion of a prevalence of approximately 4.9 in 10.000 is in line with prior designation and was considered acceptable. The oral explanation was cancelled.

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 DNA plasmid encoding IL-12 p35 and p40 genes was considered justified based on non-clinical data showing reduction of tumour size and improved survival, and on preliminary clinical data showing responses in patients with relapsed disease.

The condition is chronically debilitating 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 approximately 4.9 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 provided sufficient justification for the assumption that the medicinal product containing DNA plasmid encoding IL-12 p35 and p40 genes will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data that demonstrate responses in patients relapsing from the condition, and in newly diagnosed ovarian cancer in combination with standard of care. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for DNA plasmid encoding IL-12 p35 and p40 genes, for treatment of ovarian cancer, was adopted by consensus.

2.1.2. - EMA/OD/0000020629

Treatment of small cell lung cancer (SCLC)

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 whether there exists a scientific rationale for the development of the proposed product for Treatment of small cell lung cancer (SCLC) the sponsor should further elaborate on the methodology used in the in vivo pre-clinical studies as well as the results from these studies and their relevance for the development of the product in the condition.

In particular, the addition of observations from independent experiment(s) in the control group of the xenotransplantation model is viewed as problematic and should be justified. The sponsor was asked to discuss the relevance of the endpoints studied in the in vivo experiment.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. However, the COMP noted the absence of data to justify a clinically relevant advantage or a major contribution to patient care versus the authorised products.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from any in vivo non-clinical or clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan condition.

In the written response, and during an oral explanation before the Committee on 17 March 2020, the sponsor addressed the raised issues as follows. With regards to the medical plausibility, the data from the in vivo experiment were presented again. A non-statistical trend in reduction of tumour weight for the studied doses was argued, but no statistical considerations could be made. As for the significant benefit, the applicant discussed in vitro synergy in various SCLC cell lines in combination to carboplatin.

The Committee considered that in the absence of in vivo observations to justify both criteria, the proposal would not be acceptable at this point in time. It has been considered in the past that such level of observations is important in particular for oncological applications, as aspects including immunological and angiogenic responses that play a role in tumour behaviour cannot be studied in the in vitro culture settings proposed.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 March 2020, prior to final opinion.

2.1.3. tislelizumab - EMA/OD/0000021732

BeiGene Ireland Limited; Treatment of hepatocellular carcinoma

COMP Rapporteur: Brigitte Schwarzer-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:

- Prevalence

The sponsor was invited to provide a justification of the disease duration and discuss if a 5-year prevalence is adequate to estimate the number of affected individuals, given that the identified median survival seems to be significantly lower.

The sponsor was invited to further justify the proportion of HCC (hepatocellular carcinoma) amongst all liver cancer as reported in ECIS.

The sponsor was invited to provide an alternative estimation of prevalence on the basis of crude annual incidence reported in ECIS taking into consideration the proportion of HCC and the median disease duration.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit:

- To further justify the validity of the provided indirect comparisons in second line treatment by discussing similarities and differences of compared patient populations. In this context, the sponsor was asked to clarify if the enrolled patients in the ongoing development were screened and/or selected for biomarker PD-1/PD-L1.
- To further discuss the indirect efficacy comparison in second line to the most recent data on the comparator therapies. Especially, regorafenib seems to have overall similar therapeutic efficacy in terms of ORR (objective response rate).
- To further elaborate on the patient population in third line and if these patients have received the best standard of care including the currently authorised second line therapies.

In the written response, the sponsor elaborated on the issues that were identified by the COMP. It was clarified that the proposed prevalence for HCC would be 0.28 to 0.51 per 10,000 depending on the data source. These estimates were based on annual incidence from different cancer registry databases. The sponsor justified the use of incidence, because the proposed condition has a 1-year disease duration. The data provided by the sponsor on median survival however suggested a longer disease duration in at least some of the patients. Hence the provided incidence estimates seemed not to be sufficient to estimate prevalence of the condition. The COMP took into account the submitted evidence by the sponsor on incidence and median survival and decided to designate a prevalence of approximately 1 per 10,000. This estimated prevalence took into account the upper limit of annual incidence of 0.51 and an assumed disease duration of up to 2 years.

Regarding significant benefit, the sponsor outlined that most enrolled third line patients did not receive the currently authorised second line therapies. For the demonstration of significant benefit in second line HCC, the sponsor provided additional justifications on the comparability of the patient characteristics that have been used for indirect comparison. The sponsor also updated the outcome of the indirect comparison by making sure that the same response criteria were used to compare responses observed in different trials.

The COMP considered that this level of evidence was sufficient to support the assumption of significant benefit for the purpose of initial orphan designation, and the oral explanation was cancelled.

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

The intention to treat the condition with the medicinal product containing tislelizumab was considered justified based on preliminary clinical data demonstrating anti-tumour responses in patients affected by the condition.

The condition is chronically debilitating and life-threatening due to increased mortality and liver dysfunction. Median survival without therapy can be approximately 36 months for stage 0 and A, 16 months for stage B, 4-8 months for stage C and less than 4 months for stage D.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tislelizumab will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data demonstrating anti-tumour responses in patients affected by the condition. High-level indirect comparisons suggest that the observed clinical responses compare favourable to clinical responses of currently authorised products in second line therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tislelizumab, for treatment of hepatocellular carcinoma, was adopted by consensus.

2.1.4. haematopoietic stem cells and blood progenitors umbilical cord-derived expanded with (1R, 4R)-n1-(2-benzyl-7-(2-methyl-2h-tetrazol-5-yl)-9H-pyrimido[4,5-b]indol-4-yl)cyclohexane-1,4-diamine dihydrobromide dihydrate - EMA/OD/0000022351

CATS Consultants GmbH; Treatment in haematopoietic stem cell transplantation

COMP Rapporteur: Martin Mozina

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 sponsor should change the condition to treatment in haematopoietic stem cell transplantation as this would fit more adequately the proposed uses of the product than the submitted indication of prevention of Graft vs Host Disease. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00).

The sponsor was requested to provide more information on the mode of action of the proposed product and how it expands the umbilical cord blood cells.

- Number of people affected

The sponsor provided a prevalence calculation for a subset namely patients who would receive an allogeneic haematopoietic stem cell transplantation. The sponsor was requested to recalculate the whole prevalence for those who would be eligible for treatment in haematopoietic stem cell transplantation.

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". In the written response, the sponsor amended the condition to "treatment in haematopoietic stem cell transplantation" as requested by the COMP. The prevalence was re-estimated as requested to a final value of 0.7 in 10,000 which the COMP accepted. The sponsor also elaborated on the mechanism of action of the proposed product, revolving around the activation of a novel E3 Ligase.

Following review of the application by the Committee, it was agreed to rename the condition to treatment in haematopoietic stem cell transplantation.

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

The intention to treat the condition with the medicinal product containing haematopoietic stem cells and blood progenitors umbilical cord-derived expanded with (1R, 4R)-N1-(2-benzyl-7-(2-methyl-2H-tetrazol-5-yl)-9H-pyrimido[4,5-b]indol-4-yl)cyclohexane-1,4-diamine dihydrobromide dihydrate was considered justified based on preliminary clinical data showing improved engraftment.

The condition is life-threatening and chronically debilitating due to susceptibility to severe infections and complications such as graft-versus-host disease.

The condition was estimated to be affecting approximately 0.7 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 exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing haematopoietic stem cells and blood progenitors umbilical cord-derived expanded with (1R, 4R)-N1-(2-benzyl-7-(2-methyl-2H-tetrazol-5-yl)-9H-pyrimido[4,5-b]indol-4-yl)cyclohexane-1,4-diamine dihydrobromide dihydrate will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data that demonstrate a better outcome than other allogenic stem cell transplantations. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for haematopoietic stem cells and blood progenitors umbilical cord-derived expanded with (1R, 4R)-N1-(2-benzyl-7-(2-methyl-2H-tetrazol-5-yl)-9H-pyrimido[4,5-b]indol-4-yl)cyclohexane-1,4-diamine dihydrobromide dihydrate, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.5. - EMA/OD/0000022586

Treatment of von Hippel-Lindau disease

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 whether there exists a scientific rationale for the development of the proposed product for treatment of von Hippel-Lindau disease the sponsor was requested to further elaborate on the lack of any data in the condition with the product applied for and the significance of the bridging exercise to the data generated with another active

substance. The extrapolation provided involved another condition and it was considered inadequate for the purpose of establishing medical plausibility.

In the absence of data with the proposed product in the sought condition, medical plausibility could not be established.

In the written response, and during an oral explanation before the Committee on 18 March 2020, the sponsor did not provide any in vivo data in a model of the proposed condition or in affected patients. The sponsor further elaborated on in vitro data using cells from patients which supported induction of apoptosis, and on the bridging exercise with data from another active substance. The COMP concluded that insufficient data had been submitted to support the recommendation to grant an orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 March 2020, prior to final opinion.

2.1.6. - EMA/OD/0000022633

Prevention of retinopathy of prematurity

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 whether there exists a scientific rationale for the development of the proposed product for prevention of retinopathy of prematurity the sponsor was requested to further elaborate on:

  - The relevance of the nonclinical models used for the prevention of retinopathy of prematurity, with regards to the intended scope (prevention rather than treatment), and relevance of studied endpoints.
  - The methodology used in the pre-clinical studies as well as the results from these studies and their relevance for the development of the product in the condition.

- Number of eligible patients

The sponsor was asked to further elaborate on the use of gestational age of less than 32 weeks to define the number of patients eligible for prevention. A sensitivity analysis of any assumptions used (such as gestational age or birth weight) was expected to be included in the discussion.

In the written response, and during an oral explanation before the Committee on 18 March 2020, the sponsor submitted a revised estimation of the number of eligible patients which was considered acceptable by the COMP. The sponsor also elaborated on the relevance of two published articles in non-clinical models in support of the medical plausibility, discussing the settings and studied endpoints. The COMP remained sceptical with regards to the relevance of the publications. The first publication was studying the effects on retinal hypoxia which was not deemed to be a model of the condition per se, while the second was not showing any effects on vascular proliferation. Therefore, the intention to prevent the proposed condition was not considered to have been justified.

In communicating to the sponsor, the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 March 2020, prior to final opinion.

2.1.7. - EMA/OD/0000022802

Treatment of acute myeloid leukaemia

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

For the demonstration of intention to treat for the purpose of orphan designation, the sponsor was requested to present additional and more mature clinical data demonstrating efficacy in the condition. In the absence of additional and more mature clinical data, the intention to treat cannot be established.

- Significant benefit

For the demonstration of significant benefit for the purpose of orphan designation, the sponsor was asked to present additional and more mature clinical data demonstrating efficacy in relapsed refractory AML (acute myeloid leukaemia) patients. In the absence of additional and more mature clinical data, significant benefit cannot be established.

In the written response, and during an oral explanation before the Committee on 17 March 2020, the sponsor provided additional data of two patients that were treated in the currently ongoing clinical trial. No formal efficacy assessment could be performed in one of the two patients. The other patient showed a reduction in bone marrow blast count but did not achieve a clinical response. The COMP noted an overall heterogeneous patient population that had so far been treated with different dosages and regimens. This might also explain the differences observed in the outcomes of patients. Overall, the available efficacy dataset was characterised by only one patient, who achieved a clinical response. The COMP considered that the provided level of evidence was not sufficient to support the intention to treat for the purpose of orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 March 2020, prior to final opinion.

2.1.8. - EMA/OD/0000022808

Treatment of intrahepatic cholestasis of pregnancy

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 whether there exists a scientific rationale for the development of the proposed product for treatment of intrahepatic cholestasis of pregnancy the sponsor was requested to further elaborate on:

  - The lack of data in the condition with their product and the relevance of the bridging exercise between data generated in NASH (non-alcoholic steatohepatitis) with their product and the condition.
  - There appears to be a non-clinical model of the condition which is associated with the condition. The sponsor was requested to further elaborate why they did not use such model.

- Significant benefit

The arguments on significant benefit are based on an alternative mechanism of action and the potential improved efficacy in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the relevance of the bridging data to justify the assumption of significant benefit over authorised medicinal products (ursodeoxycholic acid) for the proposed orphan condition. Alternatively, they should explain if they have any non-clinical in vivo data in a model of the condition which could support the claim for significant benefit.

In writing and during an oral explanation, the sponsor defended the lack of non-clinical in vivo data in a model of the condition or preliminary clinical data, on the grounds that the product does not enter the body but remains localised in the intestinal tract. For this reason, the sponsor was of the opinion that the bridging exercise in other conditions adequately supported the medical plausibility. The COMP considered that data in the specific condition as applied for designation would be needed, which was not currently available. In the absence of such data, the COMP was of the of the opinion that they could not recommend granting the orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 March 2020, prior to final opinion.

2.1.9. rozanolixizumab - EMA/OD/0000022918

UCB Pharma; Treatment of myasthenia gravis

COMP Rapporteur: Darius Matusevicius

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 used data from publications spanning the last 70 years to estimate the prevalence.

The sponsor was requested to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition and the calculation should be focused on more recent publications.

- Significant benefit

The sponsor presented data from the Phase 2 study showing transient effects of the product in mild, moderate and severely affected patients with myasthenia gravis. Only three patients with severe myasthenia gravis (MG) were included.

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition when used in patients experiencing disease flare ups and not categorised as treatment refractory yet.

To support significant benefit the sponsor was requested to further clarify the clinical study design and inclusion criteria. In addition, the sponsor was asked to present data to support the potential efficacy in patients affected by MuSK (muscle-specific receptor kinase)-autoimmunity.

The sponsor was requested to explain whether the additional effects of rozanolixizumab in combination with eculizumab will be studied, and if any effect could be expected.

The sponsor was asked to detail the results of any clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

Furthermore, it would be useful to obtain more information on the ongoing study/planned development.

In the written response, the sponsor provided a refined calculation of prevalence, which focused on the most recent sources of data. The revised estimate remained at 2 in 10,000 persons in the EU.

In addition, the sponsor discussed in detail the arguments for significant benefit of rozanolixizumab over the standard of care. The sponsor clarified the intended position of the treatment on top of the standard of care in patients who otherwise would receive IVIG (intravenous immunoglobulin) or plasma exchange treatment to complement treatment with immunosuppressants. The sponsor clarified that the product is not developed in patients refractory to treatment who would otherwise be eligible to treatment with eculizumab. However, potential of extending treatment to refractory patients who are affected by MuSK-MG was proposed and supported by data from one MuSK-MG patient who responded to treatment with rozanolixizumab. The COMP considered this data anecdotal in nature, and focused on the data presented in support of efficacy in combination with the standard of care. To this end, the data was accepted because the sponsor provided placebo-controlled data and confirmed that no rescue medication was used in the active treatment arm of the study. Considering the presented data, and that the planned phase 3 study supports the proposed positioning of the product, the COMP considered the answers of the sponsor satisfactory. The oral hearing was therefore cancelled.

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

The intention to treat the condition with the medicinal product containing rozanolixizumab was considered justified based on early clinical data showing positive responses on myasthenia gravis specific outcome measures.

The condition is life-threatening and chronically debilitating due to muscle weakness affecting in particular muscles that control eye and eyelid movement, facial expressions, chewing, talking, and swallowing. Recurrent myasthenic crisis can also affect muscles that control breathing, resulting in life-threatening respiratory impairment.

The condition was estimated to be affecting approximately 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 exist in the European Union, the sponsor provided sufficient justification for the assumption that the medicinal product containing rozanolixizumab will be of significant benefit to those affected by the condition. The sponsor provided clinical data that demonstrate that patients who were not stabilised under the standard treatment including immunosuppressants achieved improvement of myasthenia gravis symptoms. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for rozanolixizumab, for treatment of myasthenia gravis, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000009482

Treatment of retinal detachment

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

2.2.2. cusatuzumab - EMA/OD/0000018294

Janssen-Cilag International N.V.; Treatment of acute myeloid leukaemia

COMP Rapporteur: Maria Elisabeth Kalland

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 cusatuzumab was considered justified based on preliminary clinical data which showed that patients who were unfit for intensive treatment achieved complete responses.

The condition is life threatening due to several 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 approximately 1.6 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing cusatuzumab will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data that demonstrate improved overall response rates when the product was used in combination with azacitidine in patients who were unfit to receive intensive chemotherapy. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.3. - EMA/OD/0000019446

Treatment of Cushing's Disease

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

2.2.4. adeno-associated viral vector serotype 3B encoding human multidrug resistance protein 3A - EMA/OD/0000020387

Vivet Therapeutics S.A.S.; Treatment of progressive familial intrahepatic cholestasis (PFIC)

COMP Rapporteur: Elisabeth Johanne Rook

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 3B encoding human multidrug resistance protein 3A was considered justified based on non-clinical data supporting improvements in liver-biochemistry and histology in a relevant PFIC3 model.

The condition is life-threatening and chronically debilitating due to progressive severe liver dysfunction, accompanied by portal hypertension, liver failure, cirrhosis, and higher incidence of hepatocellular carcinoma.

The condition was estimated to be affecting approximately 0.2 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype 3B encoding human multidrug resistance protein 3A will be of significant benefit to those affected by the condition. The sponsor provided non-clinical data supporting durable improvements in liver function tests, bile composition and liver histology in a relevant model of the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 3B encoding human multidrug resistance protein 3A, for treatment of progressive familial intrahepatic cholestasis, was adopted by consensus.

2.2.5. - EMA/OD/0000020940

Treatment of multiple myeloma

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

2.2.6. florbetaben (^{18}F) - EMA/OD/0000021576

Life Molecular Imaging GmbH; Diagnosis of AL amyloidosis

COMP Rapporteur: Dinah Duarte

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

The intention to diagnose the condition with the medicinal product containing florbetaben (^{18}F) was considered justified based on preliminary clinical data showing sensitivity and specificity of positron emission tomography (PET) imaging with the proposed product for the diagnosis of cardiac AL amyloidosis.

The condition is chronically debilitating and life-threatening due to the accumulation of fibril deposits which disrupts normal tissue structure and function, notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues.

The population of patients eligible for diagnosis of the condition was estimated to be approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of diagnosis of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing florbetaben (^{18}F) will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data showing sensitivity and specificity of Positron Emission Tomography imaging with the proposed product for the diagnosis of cardiac AL amyloidosis. The proposed product with Positron Emission Tomography imaging could also be used for the diagnosis of AL amyloidosis patients that cannot undergo cardiac magnetic resonance imaging with currently authorised contrast agents. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for florbetaben (^{18}F), for diagnosis of AL amyloidosis, was adopted by consensus.

2.2.7. mitapivat sulfate - EMA/OD/0000022133

Agios Netherlands B.V.; Treatment of pyruvate kinase deficiency

COMP Rapporteur: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing mitapivat sulfate was considered justified based on clinical data in patients showing improvement in haemoglobin levels and reduction in markers of haemolysis.

The condition is chronically debilitating and life-threatening due to symptoms of chronic haemolytic anaemia and sequelae of periodic red blood cell transfusions, comprising fatigue, shortness of breath, splenomegaly, cholecystolithiasis, heart failure, as well as compromised immune function and thromboembolic complications after splenectomy. The condition is also life-threatening due to aggravation of haemolytic anaemia during pregnancy and aplastic crisis during viral infections, as well as hydrops fetalis and perinatal death.

The condition was estimated to be affecting less than 0.5 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for mitapivat sulfate, for treatment of pyruvate kinase deficiency, was adopted by consensus.

2.2.8. - EMA/OD/0000022335

Treatment of pericarditis

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

2.2.9. - EMA/OD/0000023090

Treatment of marginal zone lymphoma

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

2.2.10. - EMA/OD/0000023410

Treatment of multiple myeloma

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

2.2.11. - EMA/OD/0000023461

Treatment of primary sclerosing cholangitis

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

2.2.12. anti-(integrin beta-3) human monoclonal antibody - EMA/OD/0000023599

FGK Representative Service GmbH; Prevention of fetal and neonatal alloimmune thrombocytopenia (FNAIT)

COMP Rapporteur: Lyubina Racheva Todorova

Following review of the application by the Committee, it was agreed to rename the indication to prevention of fetal and neonatal alloimmune thrombocytopenia due to human platelet antigen-1a incompatibility.

The Committee agreed that the condition, fetal and neonatal alloimmune thrombocytopenia due to human platelet antigen-1a incompatibility, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing anti-(integrin beta-3) human monoclonal antibody was considered justified based on non-clinical data demonstrating improvements in pregnancy outcomes upon preventative therapy with the proposed product.

The condition is chronically debilitating and life threatening due to the occurrence of bleeding with intracranial haemorrhage which can lead to miscarriage, still birth or neonatal death or to permanent neurological damage.

The population of patients eligible for prevention of the condition was estimated to be approximately 2.5 in 10,000 persons in the European Union, at the time the application was made.

The sponsor also established that there exists no satisfactory method of prevention in the European Union for the population at risk of developing the condition.

A positive opinion for anti-(integrin beta-3) human monoclonal antibody, for prevention of fetal and neonatal alloimmune thrombocytopenia due to human platelet antigen-1a incompatibility, was adopted by consensus.

2.2.13. adeno-associated virus vector serotype hu37 encoding human factor VIII - EMA/OD/0000023893

Bayer AG; Treatment of haemophilia A

COMP Rapporteur: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing adeno-associated virus vector serotype hu37 encoding human factor VIII was considered justified based on preliminary clinical data showing sustained production of endogenous FVIII in the blood of patients treated with the proposed product, leading to reduction of bleeding episodes.

The condition is chronically debilitating due to recurrent bleeding in joints, and gastrointestinal tract and due to the risk of bleeding during trauma and surgery, which may also be life-threatening.

The condition was estimated to be affecting approximately 0.7 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus vector serotype hu37 encoding human factor VIII will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data that demonstrate that the proposed product led to sustained production of endogenous FVIII in the blood of patients treated, reducing the need of prophylactic FVIII replacement that constitutes the current standard of care. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for adeno-associated virus vector serotype hu37 encoding human factor VIII, for treatment of haemophilia A, was adopted by consensus.

2.2.14. glucagon analogue linked to a human immunoglobulin Fc fragment - EMA/OD/0000023973

JVM Europe B.V.; Treatment of insulin autoimmune syndrome

COMP Rapporteur: Robert Nistico

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

The intention to treat the condition with the medicinal product containing glucagon analogue linked to a human immunoglobulin Fc fragment was considered justified based on non-clinical models of insulin induced acute and chronic hypoglycaemia in which improvements in glucose recovery were observed.

The condition is life-threatening and chronically debilitating due to hyperinsulinemic hypoglycaemia, which can lead to seizures, learning disabilities, cerebral palsy, blindness or coma.

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 in the European Union for patients affected by the condition.

A positive opinion for glucagon analogue linked to a human immunoglobulin Fc fragment, for treatment of insulin autoimmune syndrome, was adopted by consensus.

2.2.15. - EMA/OD/0000023993

Treatment of insulinoma

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

2.2.16. - EMA/OD/0000023994

Treatment of esophageal squamous cell carcinoma

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

2.3. Revision of the COMP opinions

2.3.1. melatonin - EMA/OD/0000020769

Worphmed S.r.l.; Treatment of intracerebral haemorrhage

COMP Rapporteur: Giuseppe Capovilla

The Committee revised the negative opinion discussed during the February meeting.

A negative opinion for melatonin, for treatment of intracerebral haemorrhage, was adopted by consensus. The sponsor will have 90 days to appeal from the COMP decision.

2.3.2. benzyl benzoate, beta-caryophyllene, cineole, cinnamaldehyde, cinnamyl acetate, linalool, trans-2-methoxycinnamaldehyde - EMA/OD/0000020844

Septeos S.A.S.; Treatment of eumycetoma

COMP Rapporteur: Eva Malikova

The Committee revised the negative opinion discussed during the February meeting.

A negative opinion for melatonin, for treatment of intracerebral haemorrhage, was adopted by consensus. The sponsor will have 90 days to appeal from the COMP decision.

2.4. Amendment of existing orphan designations

None

2.5. Appeal

None

2.6. Nominations

2.6.1. New applications for orphan medicinal product designation - Appointment of COMP rapporteurs

COMP rapporteurs were appointed for seventeen applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 15 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Prevention of ischaemia reperfusion injury associated with solid organ transplantation

The Committee was briefed on the significant benefit issues.

[Post-meeting note: The COMP adopted the proposed answers on the significant benefit issues by written procedure following its March meeting.]

3.1.2. -

Treatment of naevoid basal-cell carcinoma syndrome (Gorlin syndrome)

The Committee was briefed on the significant benefit issues.

[Post-meeting note: The COMP adopted the proposed answers on the significant benefit issues by written procedure following its March meeting.]

3.2. Finalised letters

None

3.3. New requests

3.3.1. -

Treatment of Niemann-Pick disease type C

The new request was noted.

3.3.2. -

Treatment of mucopolysaccharidosis type II (Hunter syndrome)

The new request was noted.

3.3.3. -

Treatment of hepatocellular carcinoma

The new request was noted.

3.3.4. -

Treatment of diffuse large B-cell lymphoma

The new request was noted.

3.3.5. -

Treatment of pseudomyxoma peritonei (mucinous peritoneal tumour)

The new request was noted.

4. Review of orphan designation for orphan medicinal products at time of initial marketing authorisation

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

4.1.1. OFEV - nintedanib – EMEA/H/C/003821/II/0026, EMA/OD/186/12, EU/3/16/1724, EMA/OD/0000005310

MYR GmbH; Treatment of systemic sclerosis

COMP rapporteurs: Martin Mozina / Eva Malikova; CHMP rapporteur: Peter Kiely; CHMP co-rapporteur: Ewa Balkowiec Iskra

An opinion recommending not to remove OFEV, nintedanib, EU/3/16/1724 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

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

4.2.1. - pexidartinib – EMEA/H/C/004832, EMA/OD/279/14, EU/3/15/1457, EMA/OD/0000021360

Daiichi Sankyo Europe GmbH; Treatment of tenosynovial giant cell tumour, localised and diffuse type

A list of issues was adopted on 20 February 2020.

The Committee confirmed that all issues previously identified in this application had been addressed by the Applicant through the replies to the List of Questions, and therefore the oral explanation scheduled for 18 March 2020 was cancelled.

The COMP opinion on the maintenance of the orphan designation will be adopted following the CHMP opinion.

4.2.2. - bulevirtide – EMEA/H/C/004854, EMA/OD/329/14, EU/3/15/1500, EMA/OD/0000018086

Accelerated assessment

MYR GmbH; Treatment of hepatitis delta virus infection

A list of issues was adopted on 20 February 2020. An oral explanation was held on 18 March 2020.

The Committee confirmed that all issues previously identified in this application had been addressed.

The COMP opinion on the maintenance of the orphan designation will be adopted following the CHMP opinion.

4.2.3. Zolgensma - onasemnogene abeparvovec – EMEA/H/C/004750, EMA/OD/028/15, EU/3/15/1509, EMA/OD/0000003028

AveXis Netherlands B.V.; Treatment of spinal muscular atrophy

An opinion recommending not to remove Zolgensma, onasemnogene abeparvovec, EU/3/15/1509 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its March meeting.]

4.2.4. Pretomanid FGK – pretomanid – EMEA/H/C/005167, EMEA/OD/074/07, EU/3/07/513, EMA/OD/0000021750

FGK Representative Service GmbH; Treatment of tuberculosis

An opinion recommending not to remove Pretomanid FGK, pretomanid, EU/3/07/513 from the EC Register of Orphan Medicinal Products was adopted by consensus.

The orphan maintenance assessment report will be publicly available on the EMA website.

[Post-meeting note: The COMP adopted the opinion by written procedure following its March meeting.]

4.3. Appeal

None

4.4. On-going procedures

None

4.5. Orphan Maintenance Reports

None

5. Review of orphan designation for authorised orphan medicinal products at time marketing authorisation extension

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Adcetris - brentuximab vedotin - Type II variation – EMEA/H/C/002455/II/0070 - EMEA/OD/072/08, EU/3/08/595, EMA/OD/0000007448

Takeda Pharma A/S; Treatment of peripheral T-cell lymphoma

CHMP rapporteur: Paula Boudewina van Hennik

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

5.2.2. Kyprolis - carfilzomib - Type II variation - EMEA/H/C/003790/II/0045, EMA/OD/120/07, EU/3/08/548, EMA/OD/0000030043

Amgen Europe B.V.; Treatment of multiple myeloma

CHMP rapporteur: Jorge Camarero

The status of the procedure at CHMP was noted. A decision whether a formal review of the maintenance of the orphan designation is needed was postponed to April.

5.2.3. Zejula - niraparib - Type II variation - EMEA/H/C/004249/II/0019 - EMA/OD/015/10, EU/3/10/760, EMA/OD/0000031233

GlaxoSmithKline (Ireland) Limited; Treatment of ovarian cancer

CHMP rapporteur: Bjorg Bolstad

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is needed.

5.2.4. Imbruvica – ibrutinib - Type II variation - EMEA/H/C/003791/II/0059, EMA/OD/156/11, EU/3/12/984, EMA/OD/0000026247

Janssen-Cilag International NV; Treatment of chronic lymphocytic leukaemia

CHMP rapporteur: Filip Josephson

The status of the procedure at CHMP was noted.

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for two applications.

6. Application of Article 8(2) of the Orphan Regulation

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. Strategic Review & Learning meeting – COMP, 12-14 February 2020, Zagreb, Croatia

The topic was postponed.

7.1.2. Protocol Assistance Working Group (PAWG)

The meeting of the working group on Protocol Assistance was cancelled.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report from CHMP

Documents were tabled for information.

7.2.2. COMP-CAT Working Group

The meeting was held virtually on 18 March 2020.

7.2.3. COMP members nominated on EMA's recommendation

Three expressions of interest were received following the call for nomination of COMP members on EMA's recommendation. The nomination process will continue in the next months.

7.3. Coordination with EMA Working Parties/Working Groups/Drafting Groups

7.3.1. Working Party with Patients' and Consumers' Organisations (PCWP)

None

7.3.2. Working Party with Healthcare Professionals' Organisations (HCPWP)

None

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. Therapeutic Goods Administration (TGA), Australia

None

7.5.4. Health Canada

None

7.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None

7.7. COMP work plan

None

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2020 were circulated.

7.8.2. Overview of orphan marketing authorisations/applications

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

8. Any other business

8.1.1. Strategic Review & Learning meeting – joint COMP/CAT/PDCO, 21-22 November 2019, Helsinki, Finland

The Finnish member circulated a meeting memo of the joint COMP/CAT/PDCO, 21-22 November 2019 in Helsinki. Members are invited to send comments until the next meeting.

8.1.2. Committee for Orphan Medicinal Products Rules of Procedure

Due to the COVID19 public health emergency, the EMA Management Board (MB) at its meeting on 19 March 2020 adopted amendments to the existing Rules of Procedure (RoP) of all EMA's scientific committees and MB. These amendments were required to enable such bodies to continue their work in a virtual setting while adapting to the measures in place to contain the COVID19 outbreak, as well as to ensure the validity of the various decisions that each scientific committee and/or the MB will adopt in the coming weeks.

The COMP agreed to adopt the update of the RoP via written procedure.

[Post-meeting note: In view of the questions put forward during the written procedure, the COMP agreed to postpone the adoption of the updated COMP RoP to the April plenary meeting to give the COMP members the opportunity to exchange within the plenary.]

9. Explanatory notes

The notes below give a brief explanation of the main sections and headings in the COMP agenda and should be read in conjunction with the agenda or the minutes.

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

Orphan Designation *(section 2 Applications for orphan medicinal product designation)*

The orphan designation is the appellation given to certain medicinal products under development that are intended to diagnose, prevent or treat rare conditions when they meet a pre-defined set of criteria foreseen in the legislation. Medicinal products which get the orphan status benefit from several incentives (fee reductions for regulatory procedures (including protocol assistance), national incentives for research and development, 10-year

market exclusivity) aiming at stimulating the development and availability of treatments for patients suffering from rare diseases.

Orphan Designations are granted by Decisions of the European Commission based on opinions from the COMP. Orphan designated medicinal products are entered in the Community Register of Orphan Medicinal Products.

Protocol Assistance *(section 3 Requests for protocol assistance with significant benefit question)*

The protocol assistance is the help provided by the Agency to the sponsor of an orphan medicinal product, on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product in view of the submission of an application for marketing authorisation.

Sponsor

Any legal or physical person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product.

Maintenance of Orphan Designation *(section 4 Review of orphan designation for orphan medicinal products for marketing authorisation).*

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 17-19 March 2020 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Chair	Netherlands	No interests declared	
Armando Magrelli	Member (Vice-Chair)	Italy	No interests declared	
Brigitte Schwarzer-Daum	Member	Austria	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No interests declared	
Vasileios Loutas	Member	Cyprus	No interests declared	
Lenka Kovarova	Member	Czech Republic	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Cecile Dop	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Zsofia Gyulai	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Robert Nistico	Member	Malta	No interests declared	
Elizabeth Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Gloria Maria Palomo Carrasco	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Bruno Sepodes	Member	Expert recommended by EMA	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No restrictions applicable to this meeting	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Virginie Hivert	Expert*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Meeting run with support from relevant EMA staff				

* Experts were only evaluated against the agenda topics or activities they participated in.