5 December 2019
EMA/COMP/597430/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 05-07 November 2019

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

05 November 2019, 09:00-19:15, room 2A

06 November 2019, 08:30-19:30, room 2A

07 November 2019, 09:00-14:00, room 2A

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).

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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 the restricted involvement of some meeting participants in upcoming discussions as included in the pre-meeting list of participants and restrictions.

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. 23 or more members were present in the room). All decisions, recommendations and advice were agreed by consensus, unless otherwise specified.

1.2. Adoption of agenda

The agenda for 5-7 November 2019 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 8-10 October 2019 were adopted via written procedure with no amendments and will be published on the EMA website.

2. Applications for orphan medicinal product designation

2.1. For opinion

2.1.1. efgartigimod alfa - EMA/OD/0000010330

Argenx B.V.B.A.; Treatment of immune thrombocytopenia

COMP Rapporteur: Lyubina Racheva Todorova

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 an alternative mechanism of action and the potential improved efficacy in the condition.

The sponsor was requested to further elaborate on the results of the Phase II clinical data submitted to support the significant benefit assumption in the context of the current therapeutic management of patients. Of particular interest was the response in the chronic

ITP (immune thrombocytopenia) patients who have been previously treated with authorised medicines.

In the written response, the sponsor provided additional data to support the effect of their product in patients with relapsed-refractory chronic immune thrombocythemia. The COMP considered this data sufficiently compelling to cancel the oral explanation and recommend designating the product for this condition.

The Committee agreed that the condition, treatment of immune thrombocytopenia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing efgartigimod alfa was considered justified based on preliminary clinical data in patients with the condition showing an improvement in platelet counts.

The condition is chronically debilitating due to bleeding episodes and life-threatening due to events such as intracranial haemorrhage.

The condition was estimated to be affecting approximately 1.8 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 efgartigimod alfa will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data that demonstrated an improvement in platelet counts in patients with chronic immune thrombocytopenia refractory to previous lines of treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for efgartigimod alfa, for treatment of immune thrombocytopenia, was adopted by consensus.

2.1.2. lactobacillus plantarum - EMA/OD/0000014060

MDC RegAffairs GmbH; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Robert Nistico

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:

The clinical relevance of the presented outcomes and the statistical analyses in light of the high heterogeneity of the study group and the low number of enrolled patients; specifically, also present the results of the motor-function domain of the ALSFRS-R scale (the amyotrophic lateral sclerosis functional rating scale).

The concomitant therapies that patients might have received including riluzole and antibiotics. Antibiotics could alter the gut environment and the response to probiotics.

The results of the ALS-QOL endpoint.

The methodology and degree of data imputation that was needed for the generation of the comparator baseline and disease progression.

The similarities and differences between the enrolled study group and the external PRO-ACT database. In the written response, and during an oral explanation before the Committee on

5 November 2019, the sponsor clarified that the proposed product contains the probiotic *Lactobacillus plantarum* as active ingredient and a prebiotic bacterial sugar with a long history of use in foods as excipient. The sponsor provided a new analysis of the data from the presented trial, which suggests a reduction in decline on the clinical ALSFRS-R score when comparing the data from the observation period to a trendline that was based on patient data on disease progression before enrolment. The COMP discussed the methodological limitations of the clinical data, e.g. small sample size and heterogeneity of the enrolled patient populations. The sponsor presented also more detailed case reports of patients that have reported clinically relevant improvements on certain domains of the ALSFRS-R score after therapy with the proposed product. The COMP considered that these preliminary clinical observations in a few patients were sufficient to support medical plausibility for the purpose of orphan designation.

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

The intention to treat the condition with the medicinal product containing *Lactobacillus plantarum* was considered justified based on preliminary clinical observations suggesting a slower decline in the clinical ALSFRS-R score in patients treated with the proposed product.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited to 2-3 years.

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 *Lactobacillus plantarum* will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations suggesting a slower decline in ALSFRS-R score in patients treated with the proposed product. The product therefore might be able to show effects on clinical manifestations of the condition that are not treated by the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for *Lactobacillus plantarum*, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

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

2.1.3. - EMA/OD/0000012403

Treatment of pancreatic cancer

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 21 October 2019, prior to responding to the list of issues.

2.1.4. - EMA/OD/0000013983

Treatment of GM1 gangliosidosis

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 15 October 2019, prior to responding to the list of issues.

2.1.5. pamrevlumab - EMA/OD/0000012386

Voisin Consulting S.A.R.L.; Treatment of Duchenne muscular dystrophy

COMP Rapporteur: Elisabeth Penninga

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 sponsor was requested to further discuss the non-clinical results that did not demonstrate efficacy of the proposed product in models of the condition.

The sponsor was asked to discuss the preliminary clinical data and the clinical relevance of the effect size and justify the validity of the presented indirect comparisons of the preliminary clinical data by providing more information on the similarities and differences between patient population in study FGCL-3019-079 and the patients in the published studies.

In the written response, and during an oral explanation before the Committee on 6 November 2019, the sponsor elaborated on the data submitted for the demonstration of medical plausibility. The sponsor highlighted that one non-clinical study showed positive effects of the product on motor-function. The COMP discussed with the sponsor that however, not all conducted non-clinical studies showed positive effects with the proposed product. The sponsor claimed that this can be explained by well-known intra-study and inter-study heterogeneity of the used non-clinical model. The COMP considered that some uncertainty remained regarding the non-clinical evidence, but that there was some preliminary evidence to support efficacy of the product in the non-clinical setting.

Regarding the clinical evidence, the sponsor claimed that the indirect comparisons were robust and provided further information on the similarities and differences between the patient populations of the preliminary clinical dataset and the external control studies. Patient populations showed similarities regarding the presented characteristics of age, corticosteroid use, and baseline pulmonary function. In this context, the COMP considered that the presented data from an uncontrolled study in non-ambulatory patients suggested clinical activity of the proposed product in the condition.

In conclusion, the majority of COMP considered that the totality of data sufficiently supported the assumption of medical plausibility for the purpose of initial orphan designation.

The Committee agreed that the condition, treatment of Duchenne 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 pamrevlumab was considered justified based on non-clinical observations suggesting effects in motor function and preliminary clinical data suggesting effects on pulmonary function and left ventricular ejection fraction.

The condition is life-threatening and chronically debilitating due to progressive weakness occurring throughout the proximal musculature affecting the muscles of the hips, thighs, pelvic area and shoulders and eventually affecting all voluntary muscles. This is followed by dilated cardiomyopathy and cardiac output decrease, leading to terminal respiratory or cardiac failure often by late adolescence. Patients rarely live beyond the age of 30 years.

The condition was estimated to be affecting approximately 0.8 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 pamrevlumab will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data suggesting effects on pulmonary function and left ventricular ejection fraction in a patient population that is not indicated for the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pamrevlumab, for treatment of Duchenne muscular dystrophy, was adopted by majority (24 out of 27 votes).

The divergent positions (*Brigitte Blöchl-Daum; Eva Malikova; Elisabeth Johanne Rook)* were appended to this opinion.

2.1.6. - EMA/OD/0000007338

Treatment of uveal melanoma

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.

Uveal melanoma should be justified as a distinct medical entity or a valid subset for the purposes of orphan medicinal product designation; the sponsor's attention was drawn to the Orphan regulation and relevant guidelines (especially section A of ENTR/6283/00).

In its application, the sponsor proposed that uveal and cutaneous melanoma are "…embryologically, genetically, pathologically, and clinically distinct", discussing the different origin and physiology for uveal and cutaneous melanocytes, the underpinning classification, the mutations and different behaviour of the melanoma subtypes.

The sponsor was requested to:

Elaborate on the overlap of all characteristics used to justify the issue of distinctiveness, as discussed by the sponsor.

Elaborate on the identified driver mutations also taking into consideration the genetic instability of tumours.

Address the commonalities between the two juxtaposed subtypes.

Comment on the position of other melanoma types, such as conjunctival or mucosal melanoma.

Comment on the level of expression of the pharmacological target for the proposed product in melanoma subtypes other than uveal, as well as the anticipated effects therein.

In the written response, and during an oral explanation before the Committee on 6 November 2019, the sponsor discussed the different aetiology relating to UV exposure, and the mutation profile of UM (uveal melanoma) (with a particular focus on GNAQ / GNA11 and subsequent loss of a single copy of chromosome 3, inactivating mutation of BAP1 control). The sponsor also discussed the UM cure 2020 consortium (Rodriguez et al.) position which stresses the differences with regards to epidemiology, aetiology, distinctive prognostic chromosome alterations, somatic mutations and gene expression profiles, biology, and clinical features.

The following bullet points raised by COMP were outlined:

- There may be some overlap but it is "principally limited to embryogenesis and melanocyte biology"; overlap in genetics (e.g. mutations in GNAQ or GNA11 occurs in 95% of cases of UM compared to ~5% of cutaneous melanoma) and clinical characteristics are uncommon (with difference to metastatic routes);

- There is a distinction in the driver mutations in UM stemming from different exposure to UV radiation; mutations in GNAQ or GNA11, and then progression along either monosomy 3 with loss of BAP1, or along further mutations in either SF3B1 or E1F1AX; this is juxtaposed to the high tumour mutation burden, intra-tumour heterogeneity and complex mutations in cutaneous melanoma;

- With regard to the commonalities between uveal and cutaneous melanoma, the sponsor alluded to a description of the differences, but also acknowledged commonalities linked to melanocytes, embryogenesis and biology; it was also mentioned that key driver mutations present in both types are exceptionally rare, and that the thin overlap is reflected in the absence of efficacy of treatments; the latter is in essence a benefit/risk argument that may be further elaborated in the oral explanation;

- As regards the juxtaposition of uveal melanoma versus other melanoma subtypes, the sponsor provided a discussion noting that due to the rarity of mucosal and conjunctival melanomas, the availability of direct comparative analyses was limited. Some similarities in the aetiology and level of mutational burden between UM and mucosal melanoma were observed;

- Finally, with regards to the pharmacological target, the sponsor did not refute the expression outside of the uveal melanoma setting: this was because expression of the target is a function of melanin synthesis, and as such is expressed by all melanocytes.

During the oral explanation there was a further round of questions from the COMP, revolving around distinctiveness and the acknowledgment that there may be some (limited grade of) overlap in the proposed condition versus other types of melanomas. Important highlights of the discussion include the following:

The sponsor was questioned whether there are "exclusive" features of uveal melanoma, to which the sponsor responded that biology itself precludes such exclusiveness.

The sponsor was further asked with regards to formal classification of the proposed condition; the sponsor's response was that the evidence is in favour of the proposed condition being a clearly distinct entity and despite the absence of an ICD code (international classification of diseases), the classification needs to "catch-up" with the evolution in science. Staging systems and WHO references were also cited by the sponsor as supporting their proposal.

The involved external expert recommended from the EMA, also asked the sponsor whether effects in other types of melanoma, e.g. in leptomeningeal melanoma, are observed or expected; the sponsor's response was that no data existed on that issue. The COMP considered however that effects may be expected outside of the subset on the basis of the preliminary clinical observations that included responses in cutaneous melanoma types.

Following this discussion, the COMP considered that there is some extent of overlap in all elements that are examined to define a distinct medical entity valid for orphan designation, as discussed above. The Committee also considered that effects of the product can be expected in non-uveal location of disease, and that the relevant formal classification has not evolved in a way to support the validity of the proposed orphan condition.

As such, the broader, "treatment of melanoma" indication should have been considered for this application. This indication would include all types of melanoma, and not be restricted to the uveal location.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 November 2019, prior to final opinion.

2.1.7. - EMA/OD/0000013557

Treatment of haematopoietic stem cell transplantation

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 use of the proposed product in combination with other medicines in the conditioning treatment of haematopoietic stem cell transplantation with the claim of potentially more optimal conditioning than the many other combinations available where the proposed product is not used.

The sponsor was requested to further discuss the clinically relevant advantage of the proposed product as a component as opposed to other components used in similar combinations may bring 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 6 November 2019, the sponsor elaborated on indirect comparisons based on a literature search made between different conditioning regimes for haematopoietic stem cell transplantation. The comparative data presented were from retrospective analysis between the different regimes which were published. Four comparisons were submitted between the proposed product in combination vs other similar combinations. The sponsor focused their presentation primarily on safety differences and selected endpoints, like number of days of hospitalizations and rate of infections. The COMP asked the sponsor to further elaborate on outcomes and engraftment; with the exception of one comparison where outcome measures showed superiority of engraftment, there was no significant difference between the sponsors product in combination with other similar combinations.

The sponsor discussed the relative importance of the side-effect profile and differences in infections and hospitalisation rates linked with the clinically relevant advantage comparing this to the lack of significant impact on outcome of the patients who subsequently received an engraftment. It was acknowledged that there were no prospective comparative studies

which could offer a better quality of data. As no significant benefit regarding efficacy and outcomes could be found, the COMP considered that significant benefit had not been justified and thus it 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 7 November 2019, prior to final opinion.

2.1.8. - EMA/OD/0000004414

Treatment of sickle cell 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 sickle cell disease the sponsor was asked to further elaborate on:

- The extrapolation of the single thalassaemia case to the sickle cell disease setting, knowing that the non-clinical in vivo data submitted only showed an increase in HbF (fetal haemoglobin) but not the overall impact on reducing the risk of sickling of red blood cells and the impact on vaso-occlusive crisis.

- 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 requested to further discuss the arguments provided for significant benefit and to elaborate on the results from non-clinical in vivo 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 6 November 2019, the sponsor discussed the level of data and the limitations to the bridging proposed, showing the link between improved HbF levels and patient outcomes. While the COMP acknowledged that it was impossible to show the effect of the product in a non-clinical in vivo model of the condition due to the mode of action, the bridging exercise was considered of limited value. The submission of one non-clinical in vivo study showing proof of concept of the mode of action was considered insufficient to establish medical plausibility as it should be supplemented by some data on the impact on signs and symptoms which can only be seen in another non-clinical in vivo study using a model of the condition or preliminary clinical data in a limited number of patients.

The COMP was 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 6 November 2019, prior to final opinion.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/0000005940

Treatment of myasthenia gravis

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 December meeting.

2.2.2. - EMA/OD/0000007445

Treatment of acute myeloid leukaemia

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 December meeting.

2.2.3. (E)-2-((2S,4S)-4-(((2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyltetrahydro-2h-pyran-2-yl)oxy)-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl)-10-(carboxymethyl)-1-hydroxy-13-(2-(2-(2-((e)-3-(3-((3-hydroxy-3,3 diphosphonopropyl) (methyl)amino)propoxy)benzylidene) hydrazine-1-carbonothioyl)hydrazineyl)-2-oxoethyl)-8-oxo-5-thioxo-3,4,6,7,10,13-hexaazapentadec-2-en-15-oic acid - EMA/OD/0000009960

Atlanthera; Treatment of osteosarcoma

COMP Rapporteur: Bozenna Dembowska-Baginska

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

The intention to treat the condition with the medicinal product containing (E)-2-((2S,4S)-4-(((2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl)-10-(carboxymethyl)-1-hydroxy-13-(2-(2-(2-((E)-3-(3-((3-hydroxy-3,3 diphosphonopropyl)(methyl)amino)propoxy)benzylidene)hydrazine-1-carbonothioyl)hydrazineyl)-2-oxoethyl)-8-oxo-5-thioxo-3,4,6,7,10,13-hexaazapentadec-2-en-15-oic acid was considered justified based on non-clinical data in models of the condition showing inhibition of tumour growth.

The condition is chronically debilitating in particular due to the potential of limb amputation and life-threatening with a less than a 20% long-term survival rate following recurrence.

The condition was estimated to be affecting approximately 2.8 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 (E)-2-((2S,4S)-4-(((2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl)-10-(carboxymethyl)-1-hydroxy-13-(2-(2-(2-((E)-3-(3-((3-hydroxy-3,3 diphosphonopropyl)(methyl)amino)propoxy)benzylidene)hydrazine-1-carbonothioyl)hydrazineyl)-2-oxoethyl)-8-oxo-5-thioxo-3,4,6,7,10,13-hexaazapentadec-2-en-15-oic acid will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in models of the proposed condition that show increased

inhibition of tumour growth versus existing treatments in the studied settings. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (E)-2-((2S,4S)-4-(((2R,4S,5S,6S)-4-amino-5-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)oxy)-2,5,12-trihydroxy-7-methoxy-6,11-dioxo-1,2,3,4,6,11-hexahydrotetracen-2-yl)-10-(carboxymethyl)-1-hydroxy-13-(2-(2-(2-((E)-3-(3-((3-hydroxy-3,3 diphosphonopropyl)(methyl)amino)propoxy)benzylidene)hydrazine-1-carbonothioyl)hydrazineyl)-2-oxoethyl)-8-oxo-5-thioxo-3,4,6,7,10,13-hexaazapentadec-2-en-15-oic acid, for treatment of osteosarcoma, was adopted by consensus.

2.2.4. - EMA/OD/0000010610

Treatment of autoimmune haemolytic anaemia

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 December meeting.

2.2.5. synthetic double-stranded siRNA oligonucleotide directed against SERPINA1 mRNA and containing four modified nucleosides which form a ligand cluster of four n-acetylgalactosamine residues - EMA/OD/0000014201

Dicerna Ireland Limited; Treatment of congenital alpha-1 antitrypsin deficiency

COMP Rapporteur: Armando Magrelli

The Committee agreed that the condition, treatment of congenital alpha-1 antitrypsin deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing synthetic double-stranded siRNA oligonucleotide directed against SERPINA1 mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues was considered justified based on non-clinical data demonstrating that the proposed product is able to treat the clinical pathology associated with liver disease in alpha-1 antitrypsin deficiency.

The condition is life-threatening and chronically debilitating due to the early development of lung emphysema in adults and liver disease in children and adults. In liver disease, intracellular accumulation of mutant alpha-1 antitrypsin polymers in hepatocytes causes liver inflammation leading to hepatitis with cholestasis, cirrhosis or liver scarring. Liver cancer may occur later in life. Liver transplant may be required in cases of liver failure; death may occur where transplant is unavailable.

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.

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 synthetic double-stranded siRNA oligonucleotide directed against SERPINA1 mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues will be of significant benefit to those affected by the condition. The sponsor provided non-clinical data demonstrating that the proposed product is able to treat liver disease associated with the condition. The currently authorised products for the condition do not treat liver disease associated with the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic double-stranded siRNA oligonucleotide directed against SERPINA1 mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues, for treatment of congenital alpha-1 antitrypsin deficiency, was adopted by consensus.

2.2.6. - EMA/OD/0000014361

Treatment of cystinuria

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 December meeting.

2.2.7. - EMA/OD/0000014371

Treatment of pancreatic cancer

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 December meeting.

[Post-meeting note: The COMP adopted the list of issues by written procedure following its November meeting.]

2.2.8. 5,7-dichloro-2-((ethylamino)methyl)-8-hydroxy-3-methylquinazolin-4(3h)-one mesilate - EMA/OD/0000015485

Alterity Therapeutics UK Limited; Treatment of multiple system atrophy

COMP Rapporteur: Michel Hoffmann

The Committee agreed that the condition, treatment of multiple system atrophy, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 5,7-dichloro-2-((ethylamino)methyl)-8-hydroxy-3-methylquinazolin-4(3H)-one mesilate was considered justified based on non-clinical data demonstrating that the proposed product can have positive effects on motor function.

The condition is life-threatening and chronically debilitating due to autonomic failure, parkinsonism and cerebellar ataxia.

The condition was estimated to be affecting approximately 0.34 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 5,7-dichloro-2-((ethylamino)methyl)-8-hydroxy-3-methylquinazolin-4(3H)-one mesilate, for treatment of multiple system atrophy, was adopted by consensus.

2.2.9. - EMA/OD/0000015678

Treatment of Fabry 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 December meeting.

2.2.10. 2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1h-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3h)-one - EMA/OD/0000015943

Pharma Gateway AB; Treatment of tenosynovial giant cell tumour

COMP Rapporteur: Frauke Naumann-Winter

The Committee agreed that the condition, treatment of tenosynovial giant cell tumour, localised and diffuse type, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one was considered justified based on preliminary clinical data showing a reduction in tumour volume leading to improvement in joint mobility.

The condition is chronically debilitating due to loss of function of the affected joints and the development of secondary arthritis.

The condition was estimated to be affecting approximately 1.8 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 2-(isopropylamino)-3-methyl-5-(6-methyl-5-((2-(1-methyl-1H-pyrazol-4-yl)pyridin-4-yl)oxy)pyridin-2-yl)pyrimidin-4(3H)-one, for treatment of tenosynovial giant cell tumour, localised and diffuse type, was adopted by consensus.

2.2.11. - EMA/OD/0000016160

Treatment of Gaucher 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 December meeting.

2.2.12. adeno-associated virus vector encoding human phenylalanine hydroxylase - EMA/OD/0000016202

BioMarin International Limited; Treatment of phenylalanine hydroxylase deficiency

COMP Rapporteur: Elisabeth Johanne Rook

The Committee agreed that the condition, treatment of phenylalanine hydroxylase deficiency, 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 encoding human phenylalanine hydroxylase was considered justified based on non-clinical data demonstrating that the proposed product can decrease serum phenylalanine levels.

The condition is chronically debilitating due to neurological impairment in patients who are left untreated.

The condition was estimated to be affecting less than 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 adeno-associated virus vector encoding human phenylalanine hydroxylase will be of significant benefit to those affected by the condition. The sponsor provided non-clinical data demonstrating that one single administration with the proposed product is able to decrease serum phenylalanine levels over a long follow-up period. The proposed therapy could therefore treat a wider patient population and reduce the need for regular treatment with the currently authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated virus vector encoding human phenylalanine hydroxylase, for treatment of phenylalanine hydroxylase deficiency, was adopted by consensus.

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

2.2.13. - EMA/OD/0000016302

Treatment of sickle cell 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 December meeting.

[Post-meeting note: The COMP adopted the list of issues by written procedure following its November meeting.]

2.2.14. navitoclax - EMA/OD/0000016345

AbbVie Deutschland GmbH & Co. KG; Treatment of myelofibrosis

COMP Rapporteur: Karri Penttila

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

The intention to treat the condition with the medicinal product containing navitoclax was considered justified based on preliminary clinical observations that supported a reduction in spleen size in affected patients when the product was added on to previous ruxolitinib treatment.

The condition is life-threatening and chronically debilitating in particular due to anaemia, splenomegaly, extramedullary haematopoiesis, constitutional symptoms such as fatigue, night sweats and fever, cachexia and leukaemic progression.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing navitoclax will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical observations supporting a reduction in spleen size in patients when the product was added on to previous background treatment,

including ruxolitinib. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for navitoclax, for treatment of myelofibrosis, was adopted by consensus.

2.2.15. H-Leu-Pro-Pro-Leu-Pro-Tyr-Pro-OH - EMA/OD/0000016360

AdRes EU B.V.; Treatment of amyotrophic lateral sclerosis

COMP Rapporteur: Bruno Sepodes

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

The intention to treat the condition with the medicinal product containing H-Leu-Pro-Pro-Leu-Pro-Tyr-Pro-OH was considered justified based on non-clinical and preliminary clinical data showing improved survival and reduced decline in neuromuscular function.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. The survival of the patients is usually limited to 2-3 years.

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 H-Leu-Pro-Pro-Leu-Pro-Tyr-Pro-OH will be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data that demonstrate a delay in disease progression and an improvement in survival in advanced patients treated with standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for H-Leu-Pro-Pro-Leu-Pro-Tyr-Pro-OH, for treatment of treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.16. - EMA/OD/0000016622

Treatment of ovarian cancer

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 December meeting.

[Post-meeting note: The COMP adopted the list of issues by written procedure following its November meeting.]

2.2.17. - EMA/OD/0000016648

Treatment of pancreatic cancer

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 December meeting.

2.2.18. - EMA/OD/0000016718

Treatment of primary hepatocellular carcinoma (PHC)

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 December meeting.

[Post-meeting note: The COMP adopted the list of issues by written procedure following its November meeting.]

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

2.5.1. naltrexone - EMA/OD/0000020985

Able AB; Treatment of fibromyalgia

In the grounds for appeal, and during an oral explanation before the Committee on 6 November 2019, the sponsor discussed the return of investment issues.

- The clinical study's cost was questioned in both scenarios, with and without orphan incentives. The sponsor claimed different costs of a trial with and without orphan incentives, The difference in cost for a non-orphan versus an orphan study was justified citing an article by Kesselheim AS, Myers JA, Avorn J. "Characteristics of clinical trials to support approval of orphan vs nonorphan drugs for cancer", JAMA. 2011;305(22):2320–2326. doi:10.1001/jama.2011.769. In the article an average orphan product development is claimed to be cheaper than that of a non-orphan medicine. The article compares the development of medicines in rare (orphan) and non-rare (non-orphan) cancer indications and points out vast differences in trial sizes, designs and timing of marketing authorisation, which all impact on the cost of development. However, according to the committee, this publication bared little relevance to the case of fibromyalgia, where a normal clinical trial design would be expected due to the large and heterogeneous patient population. The price per patient calculation was also not in line with the number projected by the manufacturer consulted by the sponsor.

- Specific questions about the clinical trial design were asked because the sponsor did not present any details of the planned clinical trial. This was to ascertain the proposed costs estimates by the sponsor, as part of net present value (NPV) calculation. While the sponsor insisted that 200 patients would be sufficient for the trial, he was unable to provide the committee with a sample size calculation, neither define the power of the study nor provide any details of the planned study. The sponsor did clarify that the trial would be placebo controlled and of short, 6-week duration (the long-term follow-up was not mentioned). The committee advised the sponsor to seek scientific advice to plan a trial acceptable from the regulatory perspective and highlighted the importance of following the CHMP 'Guideline on

the clinical development of medicinal products intended for the treatment of pain' when preparing future development.

- The market penetration and the prevalence of patients who are expected to take the medicine were not sufficiently justified. The sponsor estimated the target patient population based on the proportion of responders in clinical studies and a limited market penetration. A real-world scenario, which would account for more patients who would start taking the drug (also those who will not respond), was not included. No sensitivity analysis was provided to support the claimed number of consumers and hence, the estimated revenue was not convincingly justified. In addition, the sponsor assumed a lower market penetration in the appeal than in the original application (reduced from 6 to 4.35 million patients) and this change was not substantiated, neither in the writer responses nor during the oral explanation. It appears that the sponsor relied on the lower confidence interval to estimate the population of patients with fibromyalgia and the sensitivity analysis for the more conservative prevalence calculation was not provided.

- The sponsor provided two price estimates per pill depending on whether there is a risk of competitors entering the marker . The cost estimation was repeated in line with the initial application but no data from similar marketed products was presented to support the estimates of the price per pill with/without incentives. Therefore, the prices were not considered well justified, and the COMP questioned this assumption.

Having considered all arguments of the sponsor and the comments of the external expert , the COMP considered that the claim of non-return on investment was not sufficiently substantiated and therefore was not adequately justified. The COMP therefore upheld the initial negative opinion based on the inadequate justification of the non-return on investment claim.

The sponsor Able AB submitted on 21 March 2019 an application for designation as an orphan medicinal product to the European Medicines Agency for a medicinal product containing naltrexone for treatment of fibromyalgia (hereinafter referred to as "the condition"). The application was submitted on the basis of Article 3(1)(a) first paragraph of Regulation (EC) No 141/2000 on orphan medicinal products.

Having examined the grounds for appeal and the additional considerations provided during the oral explanation the COMP considered that:

The intention to treat the condition can be considered justified on the basis of preliminary clinical observations in published literature that support improvement of symptoms in patients affected by the condition;

The condition is seriously debilitating due to widespread pain that can be associated with depression and anxiety. Patients affected by fibromyalgia report a negative impact on their quality of life leading to social isolation and reduced ability to work and take part in daily activities;

However, the sponsor has failed to establish that the expected revenues from marketing of the product in the European Union are unlikely to generate sufficient return to justify the necessary investment. The sponsor proposed a number of different clinical development programs for the net present value calculations. These were not sufficiently clear to be considered for a robust net present value calculation. No adequate justifications have been provided to support the sponsor's view that costs associated with clinical development can be lower when obtaining orphan designation.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are not fulfilled.

The sponsor has established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition. Thus, the requirement under Article 3(1)(b) of Regulation (EC) No 141/2000 on orphan medicinal products is fulfilled.

The COMP concluded that the requirements laid down in Article (3)(1) (a) and (b) of Regulation (EC) No 141/2000 on orphan medicinal products are not fulfilled. The COMP therefore adopted a negative opinion by consensus and recommends the refusal of the granting of the designation of naltrexone as an orphan medicinal product for orphan condition: treatment of fibromyalgia.

2.6. Nominations

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

COMP coordinators were appointed for twenty-two applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of glioma

The discussion was postponed.

3.2. Finalised letters

3.2.1. -

Treatment of gastrointestinal stromal tumours

The finalised letter was circulated for information.

3.2.2. -

Treatment of graft-versus-host disease

The finalised letter was circulated for information.

3.2.3. -

Treatment of Duchenne muscular dystrophy

The finalised letter was circulated for information.

3.2.4. -

Treatment of amyotrophic lateral sclerosis

The finalised letter was circulated for information.

3.2.5. -

Treatment of congenital adrenal hyperplasia

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of eosinophilic esophagitis

The new request was noted.

3.3.2. -

Treatment of C3 glomerulopathy

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

None

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

4.2.1. Revlimid – lenalidomide - EMEA/H/C/000717/II/0107, EMA/OD/158/12, EU/3/12/1097, EMA/OD/0000005466

Celgene Europe BV; Treatment of follicular lymphoma

CHMP rapporteur: Alexandre Moreau; CHMP co-rapporteur: Filip Josephson

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 December meeting.

4.2.2. Isturisa (previously known as Osilodrostat) – Osilodrostat - EMEA/H/C/004821, EMA/OD/099/14, EU/3/14/1345, EMA/OD/0000003092

Novartis Europharm Limited; Treatment of Cushing's syndrome

COMP rapporteurs: Armando Magrelli/ Darius Matusevicius

An opinion recommending not to remove Isturisa, osilodrostat, EU/3/14/1345 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 November meeting.]

4.2.3. – enasidenib - EMEA/H/C/004324, EMA/OD/253/15, EU/3/16/1640, EMA/OD/0000007422

Celgene Europe B.V.; Treatment of acute myeloid leukaemia

The status of the procedure at CHMP was noted.

4.3. *[Post-meeting note:* The marketing authorisation application was withdrawn after the CHMP December meeting*]*

4.4. Appeal

None

4.5. On-going procedures

COMP co-ordinators were appointed for 3 applications.

4.6. Orphan Maintenance Reports

None

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

5.2.1. Darzalex – daratumumab - EMEA/H/C/004077/II/0030, EMA/OD/038/13, EU/3/13/1153, EMA/OD/0000010020

Janssen-Cilag International NV; Treatment of plasma cell myeloma

CHMP rapporteur: Sinan B. Sarac Jiménez; CHMP co-rapporteur: Jorge Camarero

The status of the procedure at CHMP was noted.

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for 1 application.

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 – joint COMP/CAT/PDCO, 21-22 November 2019, Helsinki, Finland

The agenda for the joint COMP/CAT/PDCO SLRM under the Finnish presidency to be held on 21-22 November was presented and agreed.

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance was postponed.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

The PRIME eligibility requests were tabled for information

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

The discussion on COMP work plan 2020 was postponed.

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2019

An updated list of all applications submitted/expected and the COMP rapporteurship distribution of valid applications submitted in 2019 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. Update on EMA organisational aspects

The COMP was updated on the EMA organisational aspects

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 05-07 November 2019 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	
Nectaroula Cooper	Member	Cyprus	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Lenka Kovarova	Member	Czech Republic	No interests declared	
Frauke Naumann-Winter	Member	Germany	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	
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	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovakia	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No participation in final deliberations and voting on:	4.2.1. Revlimid – lenalidomide - EMEA/H/C/000717/II/0107, EMA/OD/158/12, EU/3/12/1097, EMA/OD/0000005466 4.2.3. – enasidenib - EMEA/H/C/004324, EMA/OD/253/15, EU/3/16/1640, EMA/OD/0000007422
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	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Hughes Dyfrig	Expert - via telephone*	Expert recommended by EMA	No restrictions applicable to this meeting	2.5.1. naltrexone - EMA/OD/0000020985 17
Kapiteijn Ellen	Expert - via telephone*	Expert recommended by EMA	No participation in final deliberations and voting on:	2.1.6. - - EMA/OD/0000007338
Meeting run with support from relevant EMA staff				

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