19 July 2018
EMA/COMP/417627/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 19-21 June 2018

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

19 June 2018, 09:00-19:30, room 2F

20 June 2018, 08:30-19:30, room 2F

21 June 2018, 08:30-16:00, room 2F

Health and safety information

In accordance with the Agency's health and safety policy, delegates are to be briefed on health, safety and emergency information and procedures prior to the start of the 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.

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).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

1.1. Welcome and declarations of interest of members and experts

Pre-meeting list of participants and restrictions in relation to declarations of interests applicable to the items of the agenda for the COMP plenary session to be held 19-21 June 2018. See June 2018 COMP minutes (to be published post July 2018 COMP meeting).

1.2. Adoption of agenda

The agenda for COMP agenda for 19-21 June 2018 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 22-24 May 2018 were adopted 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. - EMA/OD/253/17

Treatment of pilonidal sinus disease

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, 5 June 2018, prior to responding to the list of issues.

2.1.2. - EMA/OD/024/18

Treatment in 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 applicant provided a narrative review of a number of clinical studies in which the proposed product has been used within conditioning regimens for hematopoietic stem cell transplantation (HSCT) in a variety of conditions.

The sponsor, however, has not provided a data driven comparative discussion that would allow the significant benefit of the proposed product over authorised counterparts to be substantiated. The applicant is requested to provide a structured, comparative discussion based on data demonstrating a clinically relevant advantage or a major contribution to patient care of the product over authorised counterparts taking into account the current authorisations of the active substance in the EU. If indirect comparisons are being employed, an exhaustive discussion on the comparability of populations, interventions, comparators, endpoints and trial methodologies is expected.

In the written response, and during an oral explanation before the Committee on 19 June 2018, the sponsor further elaborated on the justification of the significant benefit of the product over authorised counterparts. Taking into account current authorisations of the active substance in the EU, the sponsor provided narrative reviews attempting to substantiate a clinically relevant advantage of the active substance over busulfan and thiotepa in allogeneic HSCT. The Committee considered that the evidence presented were not adequate to support the claim of a clinically relevant advantage of the active substance over thiotepa. Additionally, the non-systematic nature of the reviews severely limited the validity of the results of the comparisons.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 20 June 2018, prior to final opinion.

2.1.3. Combination of carboplatin and sodium valproate - EMA/OD/036/18

Dr Ulrich Granzer; Treatment of glioma

COMP coordinator: Dinko Vitezic

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

- Intention to diagnose, prevent or treat

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

a) the quality characteristics of the proposed product in the context of the proposed mode of administration. The sponsor should clarify if they are developing a fixed dose combination product;

b) the contribution of the device used for delivery for the treatment of the proposed condition;

c) regarding the preliminary clinical observations, the extent of any effects that may be attributed to the proposed treatment versus the effects of radiotherapy or other products that have been used in the context of the compassionate use program;

d) regarding the preliminary clinical observations, the sponsor is requested to elaborate on the characteristics of the studied population and to submit updated data at the time of the discussion.

- Significant benefit

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

In the written response, the sponsor discussed their intention to formulate the product in artificial cerebrospinal fluid, as well as a comparison of their results versus the standard of care. The current median progression in this condition is of 6-7.5 months and survival in the area of 11-12 months. This also includes patients treated with chemotherapy, including temozolomide which is authorised for the treatment of the condition. In contrast, for the cohort of patients treated by the applicant, 12m and 14m are cited respectively.

The COMP considered that despite the limited number and uncontrolled nature of observations, a trend of improvement versus the authorised counterparts may be assumed at this early stage of development. The Committee also considered that this designation pertains to a future fixed dose combination product, and a strong recommendation to engage in a protocol assistance procedure was also voiced.

The intention to treat the condition with the medicinal product containing combination of carboplatin and sodium valproate was considered justified based on preliminary clinical observations supporting improved survival in patients affected by diffuse intrinsic pontine glioma.

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

The condition was estimated to be affecting approximately 2.6 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 provided sufficient information for the assumption that the medicinal product containing combination of carboplatin and sodium valproate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical observations supporting improved survival in patients affected by diffuse intrinsic pontine glioma. The effects compare favourably to published studies with the authorised counterparts. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for combination of carboplatin and sodium valproate, for treatment of glioma, was adopted by consensus.

2.1.4. - EMA/OD/030/18

Treatment of idiopathic pulmonary fibrosis

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

In order to justify the significant benefit of the proposed product the sponsor is invited to discuss the translatability of the *in vitro* data showing inhibition of the expression of genes involved in collagen and extracellular matrix production to the intended clinical use in idiopathic pulmonary fibrosis.

The sponsor is also invited to present and discuss any available data in *in vivo* models of the condition suggesting a potential significant benefit (e.g. comparative efficacy or improved efficacy in combination) of the proposed product in relation to pirfenidone and nintedanib, currently authorised for the condition.

In the written response, and during an oral explanation before the Committee on 19 June 2018, the sponsor presented additional non-clinical *in vivo* data to support significant benefit. The product was compared to a currently authorised product and the sponsor explained that improved efficacy could be observed. The COMP however was of the opinion

that the experiment was not conclusive and no statistical significance could be observed versus the negative control, or versus the active comparator. The previously submitted *in vitro* evidence that was collected on biomarkers was also not considered sufficient in support of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 19 June 2018, prior to final opinion.

2.1.5. Tamibarotene - EMA/OD/026/18

Lakeside Regulatory Consulting Services Ltd; Treatment of acute myeloid leukaemia

COMP coordinator: Ingrid Wang

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

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the *in vivo* and preliminary clinical studies or literature to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

This discussion should also include tretinoin which is authorised in the EU in the sought condition.

In the written response, and during an oral explanation before the Committee on 20 June 2018, the sponsor elaborated on the non-clinical xenotransplantation models discussed in the medical plausibility section, arguing improved tumour burden and increased survival when the product is combined with azacitidine, vs azacitidine alone.

The preliminary clinical observations from their ongoing clinical study, where their product is used in combination with azacitidine, were discussed. Firstly, it was noted that these were unfit patients, that would not be eligible for intensive chemotherapy. Secondly, it was argued that responses with azacitidine typically occur later than 4 weeks, and would not tend to be associated with early PR to late CR conversions. In contrast a) 3 of 4 non-acute promyelocytic leukemia (APL) acute myeloid leukaemia (AML) evaluable patients treated with the combination of tamibarotene and azacitidine experienced clinical responses with initial onset at approximately 4 weeks and b) the only evaluable non-APL AML patient treated with tamibarotene and daratumumab has shown a PRi at cycle 2 day 1.

The COMP considered that the sponsor has shown non-clinical data that support add-on effects to a hypomethylating agent, as well as preliminary clinical observations in a cohort of patients not eligible for intensive chemotherapy, who responded to such a combination treatment. The COMP considered that this can be accepted as an assumption of a clinically relevant advantage, taking into considerations the limited available options for this specific group of patients, and the particulars of the observed responses.

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 tamibarotene was considered justified based on non-clinical data supporting reduction of malignant cell burden

and improvement in survival in a model of the condition, as well as clinical data supporting responses in patients affected by the condition.

The condition is chronically debilitating in particular due to intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation, and the risk of severe infections. The condition is also life-threatening with overall 5-year relative survival with the currently available treatments of approximately 20 %.

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

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 tamibarotene will be of significant benefit to those affected by the condition. The sponsor has provided non clinical data in a model of the condition and clinical data in patients not eligible for intensive chemotherapy, supporting favourable effects when the product is combined with existing treatments. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.6. Synthetic antisense oligonucleotide directed against human dystrophin pre-mRNA - EMA/OD/032/18

Wave life Sciences Ireland Limited; Treatment of Duchenne muscular dystrophy

COMP coordinator: Elizabeth 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

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Duchenne muscular dystrophy, the sponsor should further justify as to why no non-clinical *in vivo* data or preliminary clinical data have been generated to support medical plausibility. In this context, please elaborate on the possibility to test the proposed product in a valid non-clinical *in vivo* model of the condition to establish efficacy on relevant functional endpoints.

In the written response, the sponsor presented more information as to why the proposed product could not be tested in the currently available non-clinical models of the condition. The COMP acknowledged this argumentation and accepted that there was an absence of non-clinical results to show improvements in functional outcomes upon treatment. Therefore, it was considered that the non-clinical results in exon-skipping efficacy would be sufficient to support the assumption of medical plausibility for the purpose of orphan designation. This assumption would need to be supported by clinical data at the time of review of orphan designation. The COMP strongly recommended seeking EMA protocol assistance for the future development of the proposed product.

Following review of the application by the Committee, it was agreed to rename the active substance to synthetic antisense oligonucleotide directed against human dystrophin pre-mRNA.

The Committee agreed that the condition, 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 synthetic antisense oligonucleotide directed against human dystrophin pre-messenger ribonucleic acid was considered justified based on non-clinical data demonstrating that the product induces exon 51 skipping and restoration of functional dystrophin protein.

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 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing synthetic antisense oligonucleotide directed against human dystrophin pre-mRNA will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data demonstrating that the product induces exon 51 skipping and restoration of functional dystrophin protein. Hence the product could treat patients without nonsense mutations, for whom there are currently no authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic antisense oligonucleotide directed against human dystrophin pre-mRNA, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.1.7. - EMA/OD/108/17

Treatment of abdominal aortic aneurysm

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:

- Proposed condition

Abdominal aortic aneurysms should be justified as a distinct medical entity or a valid subset. 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 Rev 04).

In that context the sponsor is invited to clarify a) the rationale for anatomical focus on abdominal aortic aneurysms and b) the rationale for excluding non-aortic aneurysms

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of abdominal aortic aneurysm, the sponsor should further elaborate on:

- the envisioned target population of the product, the particulars of the intended perioperative scheme of administration, as alluded to in the application, and the potential to target other populations in the context of the proposed condition;

- the potential effects in aneurysms in other aortic locations and in non-aortic large vessels;
- the relevance of the nonclinical model used for the treatment of abdominal aortic aneurysm, and the interpretation of the results obtained in the experiments;
- the settings and results from the cited clinical studies, in the context of the envisioned administration.

- Number of people affected

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

The applicant calculated the number of people affected on the basis incidence of rupture, which is a complication of the underlying condition proposed for designation.

Irrespectively of the justification of the condition as a distinct medical entity, literature supports that aortic aneurysms are not rare, with the estimated prevalence of abdominal aortic aneurysm (AAA) in developed countries being up to 8 percent (Norman *et al*, BMJ. 2004;329(7477):1259. Lindholt *et al*, BMJ. 2005;330(7494):750, Dalaman *et al*, up-to-date (online) March 2018, Kent *et al*, J Vasc Surg. 2010;52(3):539).

The applicant is requested to justify the claim that the proposed condition may fulfil the rarity criterion and provide a sensitivity analysis to ensure the threshold is respected.

In the written response, and during an oral explanation before the Committee on 20 June 2018, the sponsor made reference to European treatment guidelines that discuss aortic aneurysms separately. However the treatment of a subpopulation would not suffice for the delineation of a distinct medical entity, on the grounds of common histopathological and etiological elements shared between the different segments of the aorta.

Concerning the prevalence calculation, the sponsor revised the calculation from 1.4 to 2.8 per 20,000. The rationale for this is not justified as it may only include patients at risk of rupture thus only considering patients with a degree of severity. The cited Swedish paper identifies that 1.7% of patients above 65 (that is 170 per 10,000 for that age group) are affected by the condition. Therefore the calculation is not based on the totality of the patients affected by the proposed condition.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 20 June 2018, prior to final opinion

2.1.8. - EMA/OD/034/18

Treatment of epidermolysis bullosa

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 1 June 2018, prior to responding to the list of issues.

2.1.9. *Ex-vivo* fused autologous human bone marrow-derived mesenchymal stem cell with allogenic human myoblast - EMA/OD/028/18

Dystrogen Therapeutics S.A.; Treatment of Duchenne muscular dystrophy

COMP coordinator: Armando Magrelli

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

- Number of people affected

The sponsor has provided data from publications covering the prevalence in several European countries. The sponsor provides a worldwide incidence of the condition but not one which is specific to Europe or does not elaborate if there are differences. The sponsor also does not seem to consider the issue of the improvement in life expectancy of the condition.

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

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

In the written response, the sponsor conducted a systematic literature search along with a manual search of reference lists of identified articles. This was complemented with direct email contact to national Duchenne muscular dystrophy (DMD) registries in individual EU countries. The following countries provided numbers for DMD patients in their national registries: Bulgaria, Poland, Portugal and UK. Latvia, Lithuania and Norway currently do not have a national DMD patient registry. All national registry respondents who provided the sponsor with DMD patient numbers issued a disclaimer that the data did not represent the whole DMD population in their respective country. As a result the sponsor relied on the UK registry data to generate an estimate of the DMD population in the EU. The basis for this rational is that the DMD community in the UK is very active and highly involved in patient support (Duchenne UK, Treat-NMD, Catapult (Cell and Gene Therapy), Action Duchenne among others). The UK registry disclosed a total of 2500 DMD patients and reported that this number encompasses all known DMD patients in the country. The UK DMD database was used to extrapolate and estimate the patient numbers in other EU countries based on their respective populations as reported by Eurostat. It was noted that the UK population is very diverse in terms of ethnicity and race, and that DMD mainly affects Caucasians. This led the sponsor to propose amended numbers based on those reported in the UK for countries such as France, Germany, Italy, Spain, Portugal and Sweden where a similar diversity might exist. For other EU countries, the Netherlands' DMD registry was accepted as the reference. The point prevalence was calculated for 31 December 2017.

As a result of the calculation, the sponsor declared that there is a total of 19 574 DMD patients in the European Union (EU 28), Norway, Iceland and Liechtenstein. This number translates into a prevalence of 0.38 per 10,000 people. As the proposed number is very close to 0.5 in 10,000 the COMP considered that the final prevalence should be reported as this number and that they could recommend granting the orphan designation.

The Committee agreed that the condition, 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 *ex-vivo* fused autologous human bone marrow-derived mesenchymal stem cell with allogenic human

myoblast was considered justified based on non-clinical data in a model of the condition showing increased levels of dystrophin in skeletal muscle associated with an improvement of functional parameters.

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 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing dystrophin expressing chimeric cells will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical data that demonstrate an improvement in dystrophin levels and functional parameters. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for *ex-vivo* fused autologous human bone marrow-derived mesenchymal stem cell with allogenic human myoblast, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/060/18

Treatment of glioma

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 July meeting.

2.2.2. - EMA/OD/058/18

Treatment of progressive supranuclear palsy

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 July meeting.

2.2.3. - EMA/OD/051/18

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 July meeting.

2.2.4. 2'-O-(2-methoxyethyl) antisense oligonucleotide targeting microtubule-associated protein tau pre-mRNA - EMA/OD/050/18

Ionis USA Ltd; Treatment of behavioural variant frontotemporal dementia

COMP coordinator: Darius Matusevicius

The Committee agreed that the condition, behavioural variant frontotemporal dementia, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 2'-O-(2-methoxyethyl) antisense oligonucleotide targeting microtubule-associated protein tau pre-mRNA was considered justified based on non-clinical data in a model of the condition showing a reduction in tau protein concentrations, in survival and functional parameters.

The condition is life-threatening and chronically debilitating due to neurological and cognitive impairment and limited life-expectancy.

The condition was estimated to be affecting approximately 2.6 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'-O-(2-methoxyethyl) antisense oligonucleotide targeting microtubule-associated protein tau pre-mRNA, for treatment of behavioural variant frontotemporal dementia, was adopted by consensus.

2.2.5. - EMA/OD/065/18

Treatment of spinal muscular atrophy

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 July meeting.

2.2.6. Adenovirus associated viral vector serotype 2/8 containing the human *CNGA3* gene - EMA/OD/048/18

MeiraGTx UK II Limited; Treatment of achromatopsia

COMP coordinator: Armando Magrelli

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

The intention to treat the condition with the medicinal product containing adenovirus associated viral vector serotype 2/8 containing the human *CNGA3* gene was considered justified based on non-clinical data showing that treatment was able to normalise electroretinography after stimulation.

The condition is chronically debilitating due to the serious impairment of visual acuity in daylight, which is associated with limitations in normal day activities. Lack of visual acuity can be accompanied by severe photophobia, nystagmus, small central scotoma, eccentric fixation and reduced or complete loss of colour discrimination.

The condition was estimated to be affecting approximately 0.3 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 adenovirus associated viral vector serotype 2/8 containing the human *CNGA3* gene, for treatment of achromatopsia, was adopted by consensus.

2.2.7. - EMA/OD/057/18

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 July meeting.

2.2.8. - EMA/OD/070/18

Treatment of pulmonary arterial hypertension

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 July meeting.

2.2.9. - EMA/OD/046/18

Treatment of eosinophilic oesophagitis

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 July meeting.

2.2.10. - EMA/OD/072/18

Treatment of follicular 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 July meeting.

2.2.11. - EMA/OD/071/18

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 respond in writing before the Committee July meeting.

2.2.12. allogeneic bone marrow derived mesenchymal stromal cells, *ex-vivo* expanded - EMA/OD/023/18

medac Gesellschaft für klinische Spezialpräparate mbH (WEDEL); Treatment of graft-versus-host disease

COMP coordinator: Frauke Naumann-Winter

Following review of the application by the Committee, it was agreed to rename the active substance to allogeneic bone marrow derived mesenchymal stromal cells, *ex-vivo* expanded.

The Committee agreed that the condition, graft-versus-host disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing allogeneic bone marrow derived mesenchymal stromal cells, *ex-vivo* expanded was considered justified based on clinical data in patients refractory to steroids and cyclosporin, who responded to treatment.

The condition is chronically debilitating and life-threatening in particular due to intestinal inflammation causing diarrhoea, abdominal pain, nausea and vomiting, as well as due to hepatotoxicity, skin and mucosal damage, sicca syndrome, cholestasis, arthritis, obliterative bronchiolitis and the need for immunosuppression that increases susceptibility to infections.

The condition was estimated to be affecting approximately 0.16 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 allogeneic bone marrow derived mesenchymal stromal cells, *ex-vivo* expanded will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate responses in affected patients who were refractory to steroids and cyclosporin. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic bone marrow derived mesenchymal stromal cells, *ex-vivo* expanded, for treatment of graft-versus-host disease, was adopted by consensus.

2.2.13. Givinostat - EMA/OD/062/18

Italfarmaco S.p.A.; Treatment of Becker muscular dystrophy

COMP coordinator: Robert Nistico

The Committee agreed that the condition, Becker 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 givinostat was considered justified based on non-clinical data suggesting that treatment might reduce the decline in motor function.

The condition is chronically debilitating due to decline in muscle strength and ambulation, increased risk of cardiomyopathy. It can be life-threatening due to the progressive decline in respiratory and cardiac strength.

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.

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 givinostat, for treatment of Becker muscular dystrophy, was adopted by consensus.

2.2.14. - EMA/OD/056/18

Treatment of vanishing white matter

Withdrawal request on 14 June 2018.

2.2.15. Liposomal Mannose-1-phosphate - EMA/OD/055/18

Glycomine SARL; Treatment of Phosphomannomutase 2-Congenital Disorder of Glycosylation (PMM2-CDG)

COMP coordinator: Ingeborg Barisic

The Committee agreed that the condition, phosphomannomutase-2 congenital disorder of glycosylation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing liposomal mannose-1-phosphate was considered justified based on *in vitro* studies in phosphomannomutase-2 congenital disorder of glycosylation patient fibroblasts showing that the product resulted in a dose-dependent increase in GDP-Mannose as well as expression of the secreted glycoprotein biomarker intercellular adhesion molecule 1.

The condition is life-threatening due to reduced life expectancy and chronically debilitating due to failure to thrive, seizures, stroke-like episodes, cardiomyopathy, liver damage, ocular and bone involvement, a higher risk of bleeding and thrombosis.

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

The 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 liposomal mannose-1-phosphate, for treatment of phosphomannomutase-2 congenital disorder of glycosylation, was adopted by consensus.

2.2.16. - EMA/OD/063/18

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 July meeting.

2.2.17. N-acetylgalactosamine-conjugated synthetic double-stranded oligomer specific to serpin family A member 1 gene - EMA/OD/061/18

Pharma Gateway AB; Treatment of congenital alpha-1 antitrypsin deficiency

COMP coordinator: Geraldine O'Dea

The Committee agreed that the condition, 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 N-acetylgalactosamine-conjugated synthetic double-stranded oligomer specific to serpin family A member 1 gene was considered justified based on nonclinical data in relevant models of the condition showing a reduction of liver polymer deposits and of liver damage with the proposed product.

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 2.6 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 N-acetylgalactosamine-conjugated synthetic double-stranded oligomer specific to serpin family A member 1 gene will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical *in vivo* data that targets the unmet need of treating the liver disorders associated with the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-acetylgalactosamine-conjugated synthetic double-stranded oligomer specific to serpin family A member 1 gene, for treatment of congenital alpha-1 antitrypsin deficiency, was adopted by consensus.

2.2.18. - EMA/OD/037/18

Treatment of idiopathic pulmonary fibrosis

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 July meeting.

2.2.19. Recombinant human ectonucleotide pyrophosphatase/phosphodiesterase 1 fused to the Fc fragment of IgG1 - EMA/OD/053/18

Inozyme Pharma Ireland Ltd; Treatment of ectonucleotide pyrophosphatase/ phosphodiesterase 1 deficiency

COMP coordinator: Ingeborg Barisic

The Committee agreed that the condition, ectonucleotide pyrophosphatase/phosphodiesterase 1 deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant human ectonucleotide pyrophosphatase/phosphodiesterase 1 fused to the Fc fragment of IgG1 was considered justified based on nonclinical data supporting improved histology and survival in a model of the condition.

The condition is life-threatening and chronically debilitating in particular due to diffuse calcification of the large arteries and myocardial infarction leading to high rate of premature death in infancy, as well as bowing of bones that can lead short stature, degenerative joint disease, bone pain, impaired mobility in adulthood.

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

The 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 recombinant human ectonucleotide pyrophosphatase/ phosphodiesterase 1 fused to the Fc fragment of IgG1, for treatment of ectonucleotide pyrophosphatase/phosphodiesterase 1 deficiency, was adopted by consensus.

2.2.20. - EMA/OD/044/18

Treatment of hematopoietic stem cell transplant-associated thrombotic microangiopathy

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 July meeting.

2.2.21. Selumetinib - EMA/OD/045/18

AstraZeneca AB; Treatment of neurofibromatosis type 1

COMP coordinator: Bożenna Dembowska-Bagińska

The Committee agreed that the condition, neurofibromatosis type 1, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing selumetinib was considered justified based on clinical data showing tumour response in neurofibromatosis type 1 patients with plexiform neurofibromas.

The condition is life-threatening due to reduced life expectancy and chronically debilitating due to cognitive deficits and learning disabilities, scoliosis, seizures, osseous dysplasia and increased risk of developing benign and malignant neoplasms.

The condition was estimated to be affecting approximately 3 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 selumetinib, for treatment of neurofibromatosis type 1, was adopted by consensus.

2.2.22. - EMA/OD/066/18

Treatment of heregulin-positive non-small cell lung 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 July meeting.

2.2.23. - EMA/OD/041/18

Treatment of growth hormone deficiency

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 July meeting.

2.2.24. Synthetic double-stranded siRNA oligonucleotide directed against lactate dehydrogenase A mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues - EMA/OD/052/18

Dicerna EU Limited; Treatment of Primary Hyperoxaluria

COMP coordinator: Martin Možina

The Committee agreed that the condition, primary hyperoxaluria, 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 lactate dehydrogenase A mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues was considered justified based on reduction of urine oxalate concentration and kidney oxalate crystal deposits in a non-clinical model of the condition;

The condition is chronically debilitating and life-threatening, in particular because of recurrent nephrolithiasis and progressive nephrocalcinosis leading to renal damage. The majority of the patients reach end stage renal disease during the 3rd to 5th decade of life.

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

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

A positive opinion for synthetic double-stranded siRNA oligonucleotide directed against lactate dehydrogenase A mRNA and containing four modified nucleosides which form a ligand cluster of four N-acetylgalactosamine residues, for treatment of primary hyperoxaluria, was adopted by consensus.

2.2.25. Tetracosactide - EMA/OD/043/18

Mallinckrodt Specialty Pharmaceuticals Ireland Limited; Treatment of Duchenne muscular dystrophy

COMP coordinator: Elizabeth Penninga

The Committee agreed that the condition, 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 tetracosactide was considered justified based on data from a study conducted in a non-clinical *in vivo* model of the condition that demonstrate a reduction in inflammation associated with an improvement in functional parameters measured.

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 0.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing tetracosactide will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical data that demonstrate a reduction in inflammation associated with an improvement in functional parameters measured and the product can be used to treat all patients affected by the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tetracosactide, for treatment of Duchenne muscular dystrophy, was adopted by consensus.

2.2.26. - EMA/OD/039/18

Treatment of idiopathic pulmonary fibrosis

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 July meeting.

2.3. Revision of the COMP opinions

None

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 coordinators

COMP coordinators were appointed for two upcoming applications.

2.7. Evaluation on-going

Four applications for orphan designation will not be discussed as evaluation is on-going.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of Fabry disease

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

3.1.2. -

Prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy

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

3.1.3. -

Treatment of congenital hyperinsulinism

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

3.1.4. -

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

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

3.1.5. -

Treatment of multiple myeloma

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

3.1.6. -

Treatment of bronchiolitis obliterans syndrome

The Committee was briefed on the significant benefit issues in preparation of the July meeting.

3.1.7. -

Treatment of graft-versus-host disease

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

3.1.8. -

Treatment of hairy cell leukaemia

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

3.2. Finalised letters

3.2.1. -

Treatment of acute myeloid leukaemia

The finalised letter was circulated for information.

3.2.2. -

Treatment of pemphigus

The finalised letter was circulated for information.

3.2.3. -

Treatment of small cell lung cancer

The finalised letter was circulated for information.

3.2.4. -

Treatment of tuberous sclerosis

The finalised letter was circulated for information.

3.2.5. -

Treatment of acute myeloid leukaemia

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of glioma

The new request was noted.

3.3.2. -

Treatment of glioma

The new request was noted.

3.3.3. -

Treatment of glioma

The new request was noted.

3.3.4. -

Prevention of graft rejection following solid organ transplantation

The new request was noted.

3.3.5. -

Treatment of transthyretin-mediated amyloidosis

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. Vyxeos (cytarabine: daunorubicin) liposome for injection – daunorubicin/ cytarabine - EMEA/H/C/004282, EMA/OD/070/11, EU/3/11/942

Jazz Pharmaceuticals Ireland Limited; Treatment of adults with high-risk acute myeloid leukaemia (AML)

The COMP concluded that:

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

The prevalence of acute myeloid leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded to be approximately 1 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

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

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the proposed product is of significant benefit to adults with high-risk acute myeloid leukaemia as defined by therapy-related AML or AML with myelodysplasia-related changes. It was demonstrated that treatment with the proposed product led to improved overall survival when compared to the currently authorised induction chemotherapy with daunorubicin and cytarabine which is standard of care treatment in newly diagnosed patients. There was also an increased rate of haematopoietic stem cell transplantation observed, which has curative potential. The Committee concluded that this constitutes a clinically relevant advantage.

The Committee for Orphan Medicinal Products has recommended that Vyxeos, liposomal combination of cytarabine and daunorubicin, daunorubicin / cytarabine, EU/3/11/942 for treatment of acute myeloid leukaemia is not removed from the Community Register of Orphan Medicinal Products.

The draft public summary of the COMP opinion will be endorsed for publication on the EMA website.

4.2.2. The opinion was adopted by written procedure after the June meeting.Onpattro - patisiran – EMEA/H/C/004699, EMA/OD/142/10, EU/3/11/857

Alnylam UK Limited; Treatment of familial amyloid polyneuropathy

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 July meeting.

4.2.3. YESCARTA - axicabtagene ciloleucel - EMEA/H/C/004480

Kite Pharma EU B.V.

a) Treatment of primary mediastinal large B-cell lymphoma EMA/OD/078/15, EU/3/15/1553

b) Treatment of follicular lymphoma EMA/OD/135/15, EU/3/15/1579

c) Treatment of diffuse large B cell lymphoma EMA/OD/171/14, EU/3/14/1393

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 July meeting.

4.2.4. - tezacaftor / ivacaftor – EMEA/H/C/004682, EMA/OD/156/16, EU/3/17/1828

Vertex Pharmaceuticals (Europe) Ltd.; Treatment of cystic fibrosis

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 July meeting.

4.2.5. - volanesorsen – EMEA/H/C/004538, EMA/OD/180/13, EU/3/14/1249

Akcea Therapeutics UK Ltd; Treatment of familial chylomicronemia syndrome

The status of the procedure at CHMP was noted.

4.2.6. - voretigene neparvovec - EMEA/H/C/004451

Spark Therapeutics Ireland Ltd

a) Treatment of retinitis pigmentosa EMA/OD/040/15, EU/3/15/1518

b) Treatment of Leber's congenital amaurosis EMA/OD/150/11, EU/3/12/981

The status of the procedure at CHMP was noted.

4.2.7. – paclitaxel - EMEA/OD/061/06, EU/3/06/422, EMEA/H/C/004154

Oasmia Pharmaceutical AB; 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 July meeting.

4.2.8. Lenvima - Lenvatinib – Type II variation - EMEA/H/C/003727/II/0011/G, EMA/OD/287/14, EU/3/15/1460

Eisai Ltd; Treatment of hepatocellular carcinoma

CHMP rapporteur: Bart Van der Schueren; CHMP co-rapporteur: Robert James Hemmings

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 July meeting.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for one application.

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. Kalydeco – Ivacaftor - Type II variation - EMEA/H/C/002494/II/0063/G, EMEA/OD/010/08, EU/3/08/556

Vertex Pharmaceuticals; Treatment of cystic fibrosis

CHMP rapporteur: Concepcion Prieto Yerro

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 July meeting.

5.2.2. Darzalex - Daratumumab – Type II variation - EMEA/H/C/004077/II/0011, EMA/OD/038/13, EU/3/13/1153

Janssen-Cilag International N.V.; Treatment of plasma cell myeloma

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

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 July meeting.

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for one 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 meetings, 23-24 October 2018, Vienna, Austria

Action: For information

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 19 June 2018.

7.1.3. Non-Clinical Working Group

The working group on Non-Clinical met on 20 June 2018.

7.1.4. Condition Working Group

The working group on Condition met on 21 June 2018.

7.1.5. Prevalence Working Group

The working group on Prevalence met on 20 June 2018.

7.1.6. Election of COMP Chairperson

Action: For information

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Documents were circulated in MMD.

Document(s) tabled:
PRIME eligibility requests - list of adopted outcomes May 2018

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

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

Action: For information

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

Action: For information

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.4.2. Priority needs and plans for training 2018 – 2020

Scope: Understanding the training needs of members / experts involved in the work of the COMP

The topic was presented to the COMP members.

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

Action: For information

Notes: Monthly teleconference

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. The 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 coordinatorship distribution of valid applications submitted in 2018

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2018 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

None

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 19-21 June 2018 meeting.

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Bruno Sepodes	Chair	Expert recommended by EMA	No interests declared	
Brigitte Blöchl-Daum	Member	Austria	No interests declared	
Tim Leest	Member	Belgium	No interests declared	
Lyubina Racheva Todorova	Member	Bulgaria	No interests declared	
Dinko Vitezic	Member	Croatia	No restrictions applicable to this meeting	
Elena Kaisis	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	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Melinda Sobor	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Violeta Stoyanova-Beninska	Member	Netherlands	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	
Fernando Mendez Hermida	Member	Spain	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Mario Ricciardi	Member	Patients' Organisation Representative	No interests declared	
Kerstin Westermark	Member	Expert recommended by EMA	No participation in final deliberations and voting on:	2.2.21. Selumetinib - EMA/OD/045/18; AstraZeneca AB; Treatment of neurofibromatosis type 1
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*		No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

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/