22 January 2020
EMA/COMP/655129/2019
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 03-05 December 2019

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

03 December 2019, 09:00-18:45, room 2A

04 December 2019, 08:30-19:30, room 2A

05 December 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 03-05 December 2019 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 05-07 November 2019 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. adeno-associated virus serotype 2/6 encoding human alpha-galactosidase a cDNA - EMA/OD/0000015678

ERA Consulting GmbH; Treatment of Fabry disease

COMP Rapporteur: Ingeborg Barisic

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

- Number of people affected

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

The application provides an estimate on birth prevalence. The sponsor was invited to present a prevalence estimate that refers to the general population of the EU, e.g. by providing additional epidemiological sources or by taking into consideration the number of live births.

In the written response, the sponsor provided further justification with regards to the previously provided prevalence calculation. The sponsor provided the birth prevalence of Fabry disease from published sources in Italy, Austria and Hungary. The reported birth prevalence ranges from 0.75 to 2.59 cases per 10,000 live births. The sponsor assumed that this figure also adequately reflects the prevalence in the general population under the following assumptions: the number of live births and the size of the general population remains steady, Fabry disease patients have a normal life expectancy, and the figures reported from three countries can be extrapolated across the EU. The prevalence figure was also adjusted for potential under-detection of non-classical Fabry disease, which is not detected by neonatal screening. These assumptions were accepted for the purpose of orphan designation, even if the sponsor did not provide sufficient evidence to support all the assumptions. In conclusion, the COMP considered that the prevalence estimate of less than 2.6 per 10,000 would adequately capture the provided range of epidemiological figures.

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

The intention to treat the condition with the medicinal product containing was considered justified based on non-clinical data demonstrating that the proposed product can restore alpha-galactosidase-A activity leading to reduced accumulation of glycolipid globotriaosylceramide.

The condition is chronically debilitating due to recurrent episodes of severe pain that do not respond to standard analgesics, and life-threatening due to renal failure, cardiovascular and cerebrovascular complications.

The condition was estimated to be affecting less than 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus serotype 2/6 encoding human alpha-galactosidase A cDNA will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data demonstrating that one single administration of the proposed product can restore α-galactosidase-A activity over a long-term follow-up period leading to reduced accumulation of glycolipid globotriaosylceramide. The proposed therapy could therefore 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 serotype 2/6 encoding human alpha-galactosidase A cDNA, for treatment of Fabry disease, was adopted by consensus.

2.1.2. - EMA/OD/0000010610

Treatment of autoimmune haemolytic anaemia

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 13 November 2019, prior to responding to the list of issues.

2.1.3. - EMA/OD/0000016622

Treatment of ovarian cancer

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

- Number of people affected

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

The sponsor was asked to justify the epidemiological index used for the estimation of the number of affected patients, taking into consideration the duration of the disease, the risk for late relapses and the long-term morbidities associated with previous treatments.

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

- Significant benefit

The sponsor was requested to further elaborate on the studied populations, the previously received treatments and discuss the observed effects in order to justify a clinically relevant advantage or major contribution to patient care versus all authorised treatments.

In the written response, and during an oral explanation before the Committee on 3 December 2019, the sponsor presented estimates using two methodologies:

a) A revised calculation featuring a 10-year partial prevalence figure, generated with reference to four sources (NORDCAN, GE, NL, UK registries), and by making further corrections to account for non-epithelial tumours (10% subtraction) and for primary peritoneal figures (addition using SEER data). This methodology arrived at an estimate of 4.033 per 10,000 people.

b) As an additional sensitivity analysis, the sponsor used ECIS 2018 incidence (44,748 cases per year), and roughly a 4.95 year duration, to arrive to a 4.326 per 10,000 people conclusion.

The COMP considered that the duration of the proposed condition for the scope of the orphan criteria was not clearly presented and justified. This was important because the two methodologies appeared to use different duration assumptions, and if the available ECIS incidence data was to be considered in the context of longer durations, the statutory threshold could have been challenged. The position to exclude patients previously diagnosed and no longer in need of treatment, as long-term complications (e.g. surgical) may manifest in patients previously considered "cured", was also not sufficiently substantiated.

With regards to the significant benefit issue, the applicant described the studied population and the mechanism of action of the proposed product. It was discussed that, for previously treated platinum resistant patients, options remain limited and an indirect comparison with the standard of care was discussed. The sponsor argued improved remission rates compared to the expected outcomes in the studied population (the sponsor had observed ORR (overall response rate) of 35% which was juxtaposed to the standard of care having limited remission rates to approximately 12% and PFS (progression-free survival) for 3-4 months). The COMP did not consider the available clinical data robust enough to accept the argument and further observations were deemed necessary.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 4 December 2019, prior to final opinion.

2.1.4. motixafortide - EMA/OD/0000016648

Granzer Regulatory Consulting & Services; Treatment of pancreatic cancer

COMP Rapporteur: Bozenna Dembowska-Baginska

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 discuss the arguments provided for significant benefit and to elaborate on the results from the preliminary clinical study submitted to justify the assumption of significant benefit over European Union authorised medicinal products for the proposed orphan condition. In particular the sponsor was invited to disentangle the effect of their product from pembrolizumab possibly by providing individual patient data from the clinical trial.

In the written response, and during an oral explanation before the Committee on 3 December 2019, the sponsor provided a written response and oral explanation concerning the products' promise in the treatment of pancreatic cancer. The presentation helped to clarify that the product on its own did not have an effect on pancreatic cancer but when used in combination with an immune checkpoint inhibitor like pembrolizumab (not authorised in the condition) a reduction in tumour growth was observed and was associated with an improvement of mean Overall Survival of several months depending on the line of therapy. The sponsor believed that what was occurring is that chemotherapy induces tumour death, thereby reducing tumour burden and creating an opening for an immunotherapy effect. Motixafortide modulates the tumour microenvironment by increasing infiltrating T cell (TILs) and decreasing MDSC (myeloid-derived suppressor cells). The use of checkpoint inhibitors maintain/restore T-cell activity in the tumour. This was hypothesized to explain the effect seen in the clinical study. COMP considered this to offer a clinically relevant advantage.

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

The intention to treat the condition with the medicinal product containing motixafortide used in combination with an immune checkpoint inhibitor was considered justified based on preliminary clinical data in patients with the advanced condition showing partial response and stable disease.

The condition is chronically debilitating because of pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression and life-threatening with a median survival of about 6 months.

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 has provided sufficient justification for the assumption that the medicinal product containing motixafortide will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that when used in combination with an immune checkpoint inhibitor their product offered a reduction in tumour size in patients with advanced disease. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for motixafortide, for treatment of pancreatic cancer, was adopted by consensus.

2.1.5. autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene - EMA/OD/0000016302

Vertex Pharmaceuticals (Ireland) Limited; Treatment of sickle cell disease

COMP Rapporteur: Eva Malikova

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 data from ex vivo experiments with an analogous product. The in vivo data submitted with the proposed product only showed an increase in HbF (haemoglobin F) 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 ex 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 3 December 2019, the sponsor addressed both issues raised. The sponsor clarified that the guide RNA used in the published ex vivo study on cell sickling was identical to the one

intended for clinical development by the sponsor. The sponsor explained (also based on a retrospective analysis of data from patients who naturally express higher amounts of HbF) that there is an inverse relationship between the levels of HbF and the incidence of vaso-occlusive crises (VOCs). The question on medical plausibility was therefore resolved.

In addition, the sponsor presented early clinical data from one patient and presented 4-month follow-up data one the levels of haemoglobin S and HbF in this patient following transplantation of the product. The patients had severe sickle cell disease and improvement in overall haemoglobin levels as well as no occurrence of VOCs or any need for transfusions or treatment with hydroxyurea since the treatment. The assumption of significant benefit was therefore accepted. The sponsor was, however, advised to come for protocol assistance when planning further development of this product.

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

The intention to treat the condition with the medicinal product containing autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene was considered justified based on ex vivo data showing reduced cell sickling and on early clinical data showing sustained elevation of foetal haemoglobin.

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

The condition was estimated to be affecting approximately 1.3 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 autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the BCL11A gene will be of significant benefit to those affected by the condition. The sponsor provided early clinical data that demonstrated that a single treatment resulted in consistent elevation of HbF production over 4 months follow-up, which reduced the need for transfusions and any need for the use of hydroxyurea. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for autologous CD34+ hematopoietic stem cells with a CRISPR-edited erythroid enhancer region of the *BCL11A* gene, for treatment of sickle cell disease, was adopted by consensus.

2.1.6. tripotassium citrate monohydrate and potassium hydrogen carbonate - EMA/OD/0000014361

Advicenne S.A.; Treatment of cystinuria

COMP Rapporteur: Geraldine O'Dea

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

- Significant benefit

The arguments on significant benefit were based on the new formulation of known alkalising agents, the potential improved efficacy in the condition and major contribution to patient care. The sponsor was asked to explain why the results of the Harvey et al., study also applied to the modified release product.

The sponsor was asked to provide more data from one study regarding compliance and palatability of compared products which would support major contribution to patient care. Further details on the number of doses of standard of care and the product along with data on alkalisation of the urine over 24 hours could support improved efficacy.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study to justify the assumption of significant benefit over authorised medicinal products, in particular immediate release formulations of alkalising agents, penicillamine and tiopronin, for the proposed orphan condition.

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

In the written response, and during an oral explanation before the Committee on 3 December 2019, the sponsor addressed all issues raised. The sponsor reassured the committee that the products described in Harvey et al., is identical to the slow release alkalising medicine. Based on the data from this publication the COMP accepted the notion that standard formulations of alkalising agents are not providing a stable normalisation of urine pH and that both fluctuations in pH, as well as overall increase of pH to the optimal level of 7-7.5 is achieved with the use of the proposed product. In addition, the sponsor presented data with the use of the product in a different patient population, that also relies on alkalising agents as part of therapy. The data indicated the high frequency with which medications available on the market should be taken and that many patients receive suboptimal treatment for practical reasons. The assumption of improved efficacy of the proposed new formulation was therefore accepted because treatment is expected to be optimised with the use of the new formulation.

The COMP questioned the sponsor with regards to more concrete evidence of improved efficacy such as formation of kidney stones and the sponsor explained that this kind of endpoint would require an extremely long follow up period in the study. Instead, the sponsor proposed to measure the size of crystals forming in the kidneys of patients as a surrogate endpoint pointing to the risk of future stone development. The COMP recommended the sponsor to come for protocol assistance to consult future clinical development plans with the regulators.

With regards to the second line therapies available on the market, the sponsor claimed that since the product is aiming at first line treatment, the hope is that the product would reduce the need for rescue therapies such as penicillamine or tiopronin. The COMP accepted these arguments but warned the sponsor that these assumptions will have to be confirmed at the time of marketing authorisation.

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

The intention to treat the condition with the medicinal product containing tripotassium citrate monohydrate and potassium hydrogen carbonate was considered justified based on clinical data showing maintained neutral urine pH.

The condition is chronically debilitating due to early onset, persistent renal stone formation which has been associated with a higher risk of developing chronic kidney disease.

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 tripotassium citrate monohydrate and potassium hydrogen carbonate will be of significant benefit to those affected by the condition. The sponsor provided clinical data that demonstrate that the product allows for maintained neutralisation of urine pH throughout the night. This compared favourably to existing immediate release and modified release formulations of other alkalising agents. In addition, it is expected that successful control of urine alkalisation would reduce the need for rescue therapy (penicillamine and tiopronin). The Committee considered that this would constitute a clinically relevant advantage.

A positive opinion for tripotassium citrate monohydrate and potassium hydrogen carbonate, for treatment of cystinuria, was adopted by consensus.

2.1.7. - EMA/OD/0000005940

Treatment of myasthenia gravis

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 18 November 2019, prior to responding to the list of issues.

2.1.8. - EMA/OD/0000007445

Treatment of acute myeloid leukaemia

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 November 2019, prior to responding to the list of issues.

2.1.9. melatonin - EMA/OD/0000016718

Worphmed S.r.l.; Treatment of primary hepatocellular carcinoma

COMP Rapporteur: Elisabeth Johanne Rook

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 intended place of melatonin in the treatment of hepatocellular carcinoma needs to be clarified by staging and treatment line (first or second line, remaining liver function), in

order to correctly position the potential significant benefit of melatonin over established methods and authorised treatments.

The sponsor was asked to provide evidence from non-clinical in vivo and/or clinical data to justify the significant benefit over the currently authorised products.

Regarding the benefits of melatonin as adjuvant to established methods like TACE (transcatheter arterial chemoembolization), the Applicant was requested to justify the extrapolation of the study by Yan et al., 2002 to the current standard of care in the EU. The relevance of this study where oral melatonin was used to the high dosages of intravenous melatonin that are proposed in the application also needed to be justified. In addition, the sponsor was requested to further discuss the results of the study in relation to tumour response and survival.

In the written response, and during an oral explanation before the Committee on 4 December 2019, the sponsor attempted to address the issues raised by proposing to narrow down the use of melatonin in clinical development only to stage BCLC 0A and BCLC B patients for whom either surgery or TACE were the only therapeutic options, according to the ESMO treatment guideline.

In view of the claimed position of melatonin in the therapeutic regimen of patients affected by hepatocellular carcinoma (HCC), the COMP considered that significant benefit would have to be considered versus methods of treatment such as resection surgery or TACE. These are considered as satisfactory methods of treatment of HCC from a regulatory point of view.

The sponsor discussed the benefit of adding high dose melatonin to the surgery and presented a publication, in which non-clinical in vivo data suggested improved survival following radical liver resection in a non-cancer setting. The COMP found this data of poor relevance, since the data were not generated in a hepatocellular carcinoma model. In addition, the sponsor also presented data from a published clinical study in which patients who had liver surgery showed improved liver chemistry markers when having received melatonin. Again, the COMP found data on post-surgery recovery not corresponding to the condition that the sponsor applied for, because no parameters specific to HCC were measured. Therefore, the COMP considered that the sponsor failed to demonstrate significant benefit of melatonin over liver tumour resection on its own.

Further, to support significant benefit over TACE, the sponsor presented a published report from a clinical study from 1998 which indicates that patients' survival improved when melatonin was given in addition to TACE procedure. The overall response was also improved in patients, but the sponsor was not able to say how 'overall response' was defined in the said publication. Also, the survival rates of patients on TACE were shorter than those achieved with this method today, which may be due to the method itself or that the general standard of care has improved since the late 1990s. Since the methodology of the study was not clearly described and the sponsor had no additional information, the COMP could not, with certainty, accept the data as reliable. The COMP concluded that the data submitted by the sponsor and the explanations provided to support the claim of significant benefit of melatonin over TACE were insufficient.

Despite having defined the intended positioning of the product in treatment of HCC, the sponsor failed to demonstrate the significant benefit of melatonin over the standard of care.

The intent to treat the condition with a medicinal product containing melatonin was justified based on non-clinical data showing reduced tumour growth in a model of the condition.

Hepatocellular carcinoma was estimated to be affecting approximately 1.3 in 10,000 persons in the European Union, at the time the application was made.

The sponsor has established that the condition is chronically debilitating and life-threatening due to liver dysfunction and increased mortality.

In addition, while satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has not provided sufficient justification for the assumption that the medicinal product containing melatonin will be of significant benefit to those affected by the condition. The sponsor provided data from literature to support the significant benefit of add-on melatonin over transcatheter arterial chemoembolization alone, or tumour resection surgery alone. There were uncertainties regarding the transcatheter arterial chemoembolization procedure used in the published study as such, the reported outcomes, and how this corresponds to the current standard of care in the European Union. In light of these uncertainties, the data were not considered reliable. The non-clinical and clinical data presented to support the benefit of melatonin added to tumour resection was considered not representative of the intended condition. Thus, the data presented were considered insufficient to demonstrate significant benefit and the sponsor failed to resolve the uncertainties which have been identified.

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

2.1.10. - EMA/OD/0000014371

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 November 2019, prior to responding to the list of issues.

2.1.11. - EMA/OD/0000016160

Treatment of Gaucher 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, on 14 November 2019, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1. dimethyl fumarate - EMA/OD/0000010028

Consorcio Centro de Investigación Biomédica en Red, M.P.; Treatment of Adrenoleukodystrophy (X-ALD)

COMP Rapporteur: Giuseppe Capovilla

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

The intention to treat the condition with the medicinal product containing dimethyl fumarate was considered justified based on in vivo data in a model of the condition, where treatment with the product showed protection against locomotor and neuropathological impairment.

The condition is life-threatening and chronically debilitating taking into consideration the two main phenotypes with which the condition presents. Cerebral adrenoleukodystrophy is associated with behavioural abnormalities, seizures, spastic tetraplegia and cognitive decline and patients usually die within several years after the onset of symptoms. Adrenomyeloneuropathy is associated with primary adrenocortical insufficiency as well as progressive stiffness and gait disturbance, with patients dying within 20 years after the onset of symptoms.

The condition was estimated to be affecting less than 0.4 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for dimethyl fumarate, for treatment of adrenoleukodystrophy, was adopted by consensus.

2.2.2. - EMA/OD/0000010743

Treatment of amyotrophic lateral sclerosis

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 January meeting.

2.2.3. 2-(3,7-dimethyl-octa-2, 6-dienyl)-6-ethylamino-3-hydroxy-5-pentyl-[1,4]benzoquinone - EMA/OD/0000011265

Emerald Health Pharmaceuticals Espana S.L.; Treatment of Huntington's Disease

COMP Rapporteur: Nectaroula Cooper

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

The intention to treat the condition with the medicinal product containing 2-(3,7-dimethyl-octa-2, 6-dienyl)-6-ethylamino-3-hydroxy-5-pentyl-[1,4]benzoquinone was considered justified based on non-clinical in vivo data in models of the condition showing a reduction in neuronal loss in the central nervous system which was associated with a reduction in decline of motor function.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 2-(3,7-dimethyl-octa-2, 6-dienyl)-6-ethylamino-3-hydroxy-5-pentyl-[1,4]benzoquinone will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate the potential to target the underlying neurodegenerative process leading to a reduction in the loss of motor function as opposed to other treatments which are indicated for symptom relief. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-(3,7-dimethyl-octa-2, 6-dienyl)-6-ethylamino-3-hydroxy-5-pentyl-[1,4]benzoquinone, for treatment of Huntington's disease, was adopted by consensus.

2.2.4. adeno-associated virus serotype 9 vector containing human N-acetylgalactosamine-6-sulfate sulfatase gene - EMA/OD/0000013447

Esteve Pharmaceuticals S.A.; Treatment of mucopolysaccharidosis type IVA (Morquio A syndrome)

COMP Rapporteur: Zsofia Gyulai

The Committee agreed that the condition, treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome), 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 serotype 9 vector containing human N-acetylgalactosamine-6-sulfate sulfatase gene was considered justified based on non-clinical evidence demonstrating that the proposed product can restore N-acetylgalactosamine-6-sulfatase activity thereby improving mortality and morbidity associated with the condition.

The condition is life-threatening and chronically debilitating due to short stature, severe skeletal dysplasia, cervical instability and cardiorespiratory failure.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated virus serotype 9 vector containing human N-acetylgalactosamine-6-sulfate sulfatase gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical evidence demonstrating that one single administration can restore N-acetylgalactosamine-6-sulfatase activity over a long-term follow-up period thereby improving mortality and morbidity associated with the condition. The proposed product may therefore reduce the need for regular treatment with the currently authorised therapy. The Committee considered that this constituted a clinically relevant advantage.

A positive opinion for adeno-associated virus serotype 9 vector containing human N-acetylgalactosamine-6-sulfate sulfatase gene, for treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome), was adopted by consensus.

2.2.5. - EMA/OD/0000013899

Treatment of epidermolysis bullosa

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 January meeting.

2.2.6. nicardipine - EMA/OD/0000015279

Bit Pharma GmbH; Treatment of non-traumatic subarachnoid haemorrhage

COMP Rapporteur: Martin Mozina

The Committee agreed that the condition, treatment of non-traumatic subarachnoid haemorrhage, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing nicardipine was considered justified based on preliminary clinical data suggesting that the proposed product is able to reduce the incidence of vasospasm in patients affected by the condition.

The condition is life-threatening and chronically debilitating due to cerebral ischemia, hydrocephalus, intracerebral haemorrhage, interventricular haemorrhage, subdural hematoma, seizures, increased intracranial pressure, left ventricular systolic dysfunction or myocardial infarction. The condition has a high mortality rate which, at 5 years, is between 65-70%.

The condition was estimated to be occurring in approximately 1 in 10,000 persons per year 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 nicardipine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data suggesting that the proposed product is able to reduce the incidence of vasospasm in patients affected by the condition when compared to patients receiving best standard of care including the currently authorised product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for nicardipine, for treatment of non-traumatic subarachnoid haemorrhage, was adopted by consensus.

2.2.7. ziritaxestat - EMA/OD/0000017344

Galapagos N.V.; Treatment of systemic sclerosis

COMP Rapporteur: Geraldine O'Dea

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

The intention to treat the condition with the medicinal product containing ziritaxestat was considered justified based on non-clinical data demonstrating that the proposed product reduced dermal thickness and lung fibrosis.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ziritaxestat will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data demonstrating that the proposed product reduced dermal thickness and lung fibrosis. These disease manifestations are not treated with the currently authorised symptomatic therapy. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.8. - EMA/OD/0000018285

Treatment of Leber congenital amaurosis

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 January meeting.

2.2.9. - EMA/OD/0000018682

Treatment of cerebral hypoxia-ischaemia reperfusion injury after return of spontaneous circulation in cardiac arrest patients

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 January meeting.

2.2.10. setmelanotide - EMA/OD/0000018797

TMC Pharma (EU) Limited; Treatment of Alström syndrome

COMP Rapporteur: Vallo Tillmann

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

The intention to treat the condition with the medicinal product containing setmelanotide was considered justified based on early clinical data in young patients who achieved reduction of body weight and hunger.

The condition is chronically debilitating due to cone-rod dystrophy in infancy, hearing loss, childhood obesity, hyperinsulinemia and insulin resistance, type 2 diabetes, cardiomyopathy, short stature in adulthood, and progressive pulmonary, hepatic, and renal dysfunction in addition to life threatening due to cardiomyopathy and complications of morbid obesity and diabetes.

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

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

A positive opinion for setmelanotide, for treatment of Alström syndrome, was adopted by consensus.

2.2.11. romilkimab - EMA/OD/0000018998

Sanofi-Aventis Groupe; Treatment of systemic sclerosis

COMP Rapporteur: Elisabeth Johanne Rook

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

The intention to treat the condition with the medicinal product containing romilkimab was considered justified based on preliminary clinical data in patients with the condition showing a significant effect on fibrosis using a validated scoring system of the condition.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing romilkimab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate disease modification and efficacy as add-on treatment to the standard of care in patients with the diffuse form of the condition. The Committee considered that this constitutes a clinically relevant advantage.

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

2.2.12. - EMA/OD/0000019103

Treatment of acute lymphoblastic leukaemia (ALL)

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 January meeting.

2.2.13. - EMA/OD/0000019108

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 January meeting.

2.2.14. - EMA/OD/0000019154

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 January meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designation

None

2.5. Appeal

None

2.6. Nominations

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

COMP rapporteurs were appointed for fifteen applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of glioma

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

3.1.2. -

Treatment of eosinophilic esophagitis

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

3.2. Finalised letters

None

3.3. New requests

3.3.1. -

Treatment of haemophilia A

The new request was noted.

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

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

4.1.1. 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

A list of issues was adopted on 07 November 2019.

An oral explanation was held on 04 December 2019.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 5 December 2019, prior to final opinion.

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

4.1.2. Polivy - polatuzumab vedotin – EMEA/H/C/004870, EMA/OD/231/17, EU/3/18/2013, EMA/OD/0000003161

Roche Registration GmbH; Treatment of diffuse large B-cell lymphoma

An opinion recommending not to remove Polivy (EU/3/18/2013) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

4.2.1. - Onasemnogene abeparvovec – EMEA/H/C/004750, EMA/OD/028/15, EU/3/15/1509, EMA/OD/0000003028

AveXis EU Limited; Treatment of spinal muscular atrophy

The status of the procedure at CHMP was noted.

4.2.2. – givosiran – EMEA/H/C/004775, EMA/OD/125/16, EU/3/16/1731, EMA/OD/0000013235

Accelerated assessment

Alnylam Netherlands B.V.; Treatment of acute hepatic porphyria

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for one application.

4.5. Orphan Maintenance Reports

Documents were tabled for information.

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. Vyndaqel – tafamidis – EMEA/H/C/002294/X/0049/G

Pfizer Europe MA EEIG;

CHMP rapporteur: Joseph Emmerich; CHMP co-rapporteur: Bruno Sepodes

a) Treatment of familial amyloid polyneuropathy, EU/3/06/401, EMA/OD/0000024082

An opinion recommending not to remove Vyndaqel, tafamidis, EU/3/06/401, from the EC Register of Orphan Medicinal Products was adopted by consensus.

b) Treatment of senile systemic amyloidosis, EU/3/12/1066, EMA/OD/0000003853

An opinion recommending not to remove Vyndaqel, tafamidis, EU/3/12/1066, 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 opinions by written procedure following its December meeting.]

5.2.2. 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

An opinion recommending not to remove Darzalex – daratumumab U/3/13/1153 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 December meeting.]

5.2.3. Crysvita – burosumab – EMEA/H/C/004275/II/0010/G, EMA/OD/133/14, EU/3/14/1351, EMA/OD/0000023281

Kyowa Kirin Holdings B.V.; Treatment of X-linked hypophosphataemia

CHMP rapporteur: Kristina Dunder; CHMP co-rapporteur: Jayne Crowe

The status of the procedure at CHMP was noted.

5.3. Appeal

None

5.4. On-going procedures

None

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 COMP received a report on the Strategic Review & Learning meeting which was held on 21-22 November in Helsinki.

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 3 December 2019.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendation on eligibility to PRIME – report

Documents were tabled for information.

7.2.2.

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

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

The documents were tabled for information.

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

Documents were tabled for information.

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

Documents were tabled for information..

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 Committee discussed the Work Plan for 2020 and identified topic leaders. Further discussion is expected in the January meeting.

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. EMA Business Pipeline activity and Horizon scanning

The COMP received a presentation on Q4/2019 Update of the Business Pipeline report for the human scientific committees.

8.2. EMA’s move to the permanent building

The COMP received an update on the EMA’s relocation to the permanent building.

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 03-05 December 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	
Dinko Vitezic	Member	Croatia	No interests declared	
Nectaroula Cooper	Member	Cyprus	No interests declared	
Lenka Kovarova	Member	Czech Republic	No interests declared	
Elisabeth Penninga	Member	Denmark	No interests declared	
Vallo Tillmann	Member	Estonia	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Frauke Naumann-Winter	Member	Germany	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Zsofia Gyulai	Member	Hungary	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
Robert Nistico	Member	Malta	No interests declared	
Elizabeth Rook	Member	Netherlands	No interests declared	
Maria Elisabeth Kalland	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovakia	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
Darius Matusevicius	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Angelo Loris Brunetta	Member	Patients' Organisation Representative	No participation in discussion, final deliberations and voting on:	4.1.1. Revlimid – lenalidomide - EMEA/H/C/000717/II/0107, EMA/OD/158/12, EU/3/12/1097, EMA/OD/0000005466

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Julian Isla	Member	Patients' Organisation Representative	No interests declared	
Pauline Evers	Member	Patients' Organisation Representative	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Bruno Sepodes	Member	Expert recommended by EMA	No interests declared	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Meeting run with support from relevant EMA staff				

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