19 April 2018
EMA/COMP/150160/2018
Inspections, Human Medicines Pharmacovigilance and Committees Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 13-15 March 2018

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

13 March 2018, 09:00-18:30, room 2F

14 March 2018, 08:30-19:30, room 2F

15 March 2018, 08:30-13:00, room 2F

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).

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

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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 13-15 March 2018 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 13-15 February 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/187/17

Treatment of ornithine transcarbamylase deficiency (OTC)

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 discuss the availability of officinal/magistral formulations of the active substance for the treatment of the condition in the EU and if such formulations can be considered well known and safe.

The sponsor is requested to provide arguments for significant benefit of the proposed product over officinal/magistral formulations.

In the written response, and during an oral explanation before the Committee on 13 March 2018, the sponsor presented evidence on magistral/officinal formulations in France, the UK and Ireland and discussed arguments as to why treatment with officinal/magistral formulations could not be considered well-known and safe. Towards this end it was argued by the sponsor that there were published safety issues regarding hospital formulations of other active substances in other disease areas.

The COMP considered that the treatment with the active substance is currently supported by suggested European treatment guidelines (Haeberle *et al*, Orphanet J Rare Dis. 2012 May 29; 7:32) and that there is evidence from the published literature that it is commonly used in European practice. Based on this evidence the COMP concluded that officinal/magistral formulations can be considered well-known and general practice. Regarding safety, the sponsor argued on theoretical safety concerns, but had to acknowledge that there were no documented safety concerns.

The sponsor did not provide data in support of significant benefit, but argued that a medicinal product with central marketing authorisation would have benefits including GMP manufacturing and regulatory safeguards including pharmacovigilance. The COMP considered that a centralised authorisation does not constitute a significant benefit, but that non-clinical or clinical data would be needed to support a clinically relevant advantage or major contribution to patient care.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 March 2018, prior to final opinion.

2.1.2. - EMA/OD/237/17

Treatment of anaplastic thyroid 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 23 February 2018, prior to responding to the list of issues.

2.1.3. - EMA/OD/238/17

Treatment of follicular thyroid 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 23 February 2018, prior to responding to the list of issues.

2.1.4. - EMA/OD/081/17

Treatment of intestinal failure-associated liver disease

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

- Proposed condition

The sponsor is invited to elaborate on the validity of the proposed condition as a distinct medical entity in the context of orphan medicinal product designation application. A

discussion of the distinctiveness of the proposed condition in terms of pathophysiology in the absence of reference to the underlying condition is expected.

- Intention to diagnose, prevent or treat

The sponsor is invited to discuss the scope of the present application, in terms of prevention or treatment of intestinal failure-associated liver disease. This is to be considered in the context of the published clinical studies, presented in support of the medical plausibility criterion.

In the written response, and during an oral explanation before the Committee on 13 March 2018, the sponsor discussed the validity of the proposed condition and medical plausibility as requested.

Regarding the validity of the condition, steatosis and cholestasis in chronic intestinal failure patients dependent on parenteral nutrition were stressed as distinct hallmarks, and the support of a field expert was also put forward in that regard. The COMP considered that these two features have already been described in the initial application and also pointed out the absence of clear diagnostic criteria in the cited consensus papers.

The lack of an in-depth understanding of the aetiology of intestinal failure-associated liver disease was acknowledged by the applicant, and in that context the product was proposed for one of the possible causal factors. Intestinal failure-associated liver disease was argued to be distinct with regards to its own symptoms, signs, diagnostic approach and management requirements compared to those of more than 100 diseases that may lead to chronic intestinal failure. However, the COMP considered that the proposed condition can be viewed as a stage of severity of any of the underlying conditions that lead to intestinal insufficiency at first place.

The applicant also downplayed any iatrogenic considerations by a) stating that the multi-factorial model of intestinal failure-associated liver disease only includes 1 iatrogenic element and b) giving an analogy to possible vitamin deficiencies if they are not provided. At the same time, the sponsor also provided examples from Orphanet and previous COMP opinions referring to conditions that could by large be perceived as a consequence by iatrogenic interventions. The COMP considered that the proposed condition has an element of malnutrition relating to the underlying primary disease by which the patients are affected.

Regarding the question of medical plausibility, the sponsor further elaborated on the available clinical data. It was asserted cholestasis was present in the treated patients, supporting a treatment indication.

In conclusion, the COMP remained sceptical with the proposed condition being a valid condition for the purpose of EU orphan designation. The proposed condition was considered a manifestation in the context of a broader underlying intestinal disease being treated.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 March 2018, prior to final opinion.

2.1.5. - EMA/OD/214/17

Treatment of polycythemia vera

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 provide data-driven arguments for significant benefit versus all authorised products including interferon, and busulfan.

Please also further elaborate on the provided indirect comparison versus ruxolitinib.

In the written response, and during an oral explanation before the Committee on 14 March 2018, the sponsor further elaborated on the issue of significant benefit, and presented an indirect comparison of the preliminary clinical efficacy data versus the efficacy of ruxolitinib; this was considered as an acceptable argument by the COMP. The Committee also agreed with the sponsor that while interferon is used off-label it is not currently authorised in the EU and no significant benefit versus interferon would need to be established. However, the sponsor could not present sufficient data over other authorised products to suggest a significant benefit. The sponsor claimed improved safety by discussing the safety profiles of currently authorised products. The COMP however could not establish improved safety based on a limited safety data-set at this stage of development.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 March 2018, prior to final opinion.

2.1.6. - EMA/OD/247/17

Treatment of Guillain-Barré syndrome

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 February 2018, prior to responding to the list of issues.

2.1.7. - EMA/OD/194/17

Treatment of adrenal insufficiency

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 sponsor should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition and demonstrate that all aetiologies have been captured for primary AI including congenital adrenal hyperplasia. In addition, the sponsor should discuss the current literature on the prevalence of drug induced AI and discuss the impact on the presented prevalence calculation.

The sponsor should revisit the current prevalence calculation based on the above comments and given the substantial uncertainty about many of the assumptions regarding the prevalence the sponsor should perform a sensitivity analysis of the reported calculations.

- Significant benefit

Regarding the trial, the sponsor should provide further information on the methodology, patient characteristics and outcomes, including outcomes on the patient level.

The arguments on significant benefit are based on the new needle-less percutaneous mode of administration and the potential major contribution to patient care in patients affected by acute adrenal crisis. However, currently there are no data available with the new mode of administration to support significant benefit, neither in the target population (adrenal insufficiency), nor in the clinical situation (suspected or manifest adrenal crisis) to be treated. The sponsor is requested to provide data to demonstrate how this new mode of administration can overcome those limitations that were outlined in surveys of patients with adrenal crisis.

In the written response, and during an oral explanation before the Committee on 14 March 2018, the sponsor presented a revised prevalence calculation that incorporated reports on higher prevalence of Addison disease in Iceland and included a report from the Netherlands on the epidemiology of steroid-induced adrenal insufficiency. The conclusive best estimate was 4.74 per 10,000 with two types of sensitivity analyses that reported on a prevalence that was higher than the orphan threshold of 5 per 10,000. The following shortcomings were discussed: not all aetiologies of adrenal insufficiency were captured by the published literature, the epidemiology of drug-induced adrenal insufficiency could be substantially higher according to other reports, and sensitivity analyses of the underlying assumptions led to prevalence estimates above the threshold. Hence, the COMP concluded that there was substantial uncertainty regarding the presented prevalence calculation, which was not able to confirm that adrenal insufficiency fulfils the orphan criterion on prevalence.

Regarding significant benefit, the discussion evolved around the proposed major contribution to patient care that was claimed because of the novel type of administration for the proposed product. The sponsor presented a study on the potential shortcomings of the current formulations for the authorised products. However, no data with proposed product in the novel form of administration was provided in patients with the condition that could generate data that might suggest a major contribution to patient care.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 March 2018, prior to final opinion.

2.1.8. - EMA/OD/065/17

Treatment of Dravet Syndrome

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 Dravet Syndrome, the sponsor should further elaborate on:

  - the results obtained in the non-clinical and preliminary clinical data discussing the relevance of the measures used to support the effects claimed.

- Significant benefit

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

The sponsor should further elaborate on the results of preliminary clinical data to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 14 March 2018, the sponsor further elaborated on the preliminary clinical data which had been presented in their initial submission. Data covered a period of three months, and 4/5 of patients responded with a reduction in seizures when the proposed product was added on top of their anticonvulsant treatment. The medical plausibility was considered justified based on this data. With regards to the issue of significant benefit, the sponsor was asked to elaborate the responses seen when the product was given on top of stiripentol in clinical settings. The size of the reported effects was not considered supportive for the justification of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 March 2018, prior to final opinion.

2.1.9. Autologous dendritic cells pulsed with killed ovarian cancer cells and matured by TLR3 ligand *ex vivo* - EMA/OD/246/17

SOTIO a.s; Treatment of ovarian cancer

COMP coordinator: Brigitte Bloechl-Daum

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

- 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 ovarian cancer, the sponsor should further elaborate on:

  - the apparent discrepancies in efficacy between sequential administration and parallel administration of the product in trial ,

- Number of people affected

The sponsor reaches a final partial prevalence estimate based on 2012 data without taking into account trends over time.

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.

The prevalence discussion could benefit from a justification on the choice of the epidemiological index (e.g. complete prevalence/ 10 year partial prevalence/ 5 year partial prevalence) and duration of the condition, consideration of more sources for the final prevalence estimate (e.g. RARECARE), as well as discussion on survival and incidence trends overtime.

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

- Significant benefit

The sponsor is invited to discuss a) which is the target population for the proposed product b) which data are available for that population with the specific product c) which are the other available authorised products for this population and d) how do those authorised products compare in that population based on clinically relevant outcomes. When indirect comparisons are being employed, the sponsor is invited to justify in detail the validity of these comparisons.

In the written response, and during an oral explanation before the Committee on 14 March 2018, the sponsor provided a recalculation of the estimate for the prevalence of ovarian cancer in the EU. The Committee accepted the sponsor's updated estimate maintaining the view that the available evidence pool on the prevalence of ovarian cancer in the EU is evolving.

The applicant also expanded on the clinical evidence provided and further elaborated on the rationale, methodology and the results of the clinical trials performed. The sponsor focused on the use of the product administered sequentially after standard first-line chemotherapy, where the most encouraging results in the so far clinical development appear to be seen. The Committee accepted the claims of potentially improving progression free survival in these settings.

With regard to the significant benefit arguments, the Committee accepted that the sponsor has provided preliminary clinical data indicating an increase in progression free survival when the product is added to standard first line chemotherapy. The Committee also considered that this increase is observed in a subpopulation of patients where no other treatments added to standard chemotherapy are authorised and indicated.

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

The intention to treat the condition with the medicinal product containing autologous dendritic cells pulsed with killed ovarian cancer cells and matured by Toll-like receptor 3 ligand *ex vivo* was considered justified based on preliminary clinical evidence indicating increased progression-free survival when added to standard chemotherapy compared with standard chemotherapy alone.

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

The condition was estimated to be affecting approximately 4.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous dendritic cells pulsed with killed ovarian cancer cells and matured by Toll-like receptor 3 ligand *ex vivo* will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data indicating an

increase in progression-free survival when the product is added to standard first line chemotherapy over chemotherapy alone. The sponsor has also provided preliminary clinical data indicating that this increase is also observed in a subpopulation of patients where no other treatments added to standard chemotherapy are authorised and indicated. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous dendritic cells pulsed with killed ovarian cancer cells and matured by TL3 ligand *ex vivo*, for treatment of ovarian cancer, was adopted by consensus.

2.1.10. - EMA/OD/228/17

Treatment of glioma

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 are based on the new mechanism of action and the potential improved efficacy in the condition.

The clinical data used in the submission covers a period where temozolomide was not authorised for use in the condition and therefore does not reflect current management of these patients.

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

In the written response, and during an oral explanation before the Committee on 14 March 2018, the sponsor noted that they had no data to show effects of their product within the context of glioblastoma multiform and the use of temozolomide in its treatment, and discussed the place of their therapy would be within the context of anaplastic astrocytoma, indicating that temozolomide was not used in the treatment of these patients. The COMP requested preliminary *in vivo* non-clinical or clinical data in the specific setting, to support the basis of this claim for their product. In the absence of such data the criteria for designation could not be considered met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 March 2018, prior to final opinion.

2.1.11. Genetically modified replication-incompetent Herpes Simplex Virus-1 expressing collagen VII - EMA/OD/244/17

IDEA Innovative Drug European Associates Limited; Treatment of Epidermolysis Bullosa

COMP coordinator: Fernando Hermida

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:

- Intension to treat

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

- the methodology used in the non-clinical studies as well as the results from these studies and their relevance for the development of the product in the proposed condition;
- the absence of functional outcomes studied in the *in vivo* model of the condition, such as transepidermal water loss;
- the envisioned mode of topical administration, in the context of a condition that affects the whole dermal surface.

In the written response, and during an oral explanation before the Committee on 14 March 2018, the sponsor further elaborated on the relevance of the proposed mechanism of action and the outcomes of the *in vivo* model studied. It was discussed that the product is envisioned to be administered in open wounds, and it was stated that collagen VII expression at 30-50% of normal levels would be sufficient for disease correction. A concern was that still no functional endpoints had been included in the studies provided, but the importance of inducing collagen VII in the treated dermal regions as supported by the presented data was acknowledged as relevant for the justification of medical plausibility.

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII.

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

The intention to treat the condition with the medicinal product containing genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII was considered justified based on nonclinical data in a hypomorphic collagen VII model, supporting expression of collagen VII in the treated dermal regions.

The condition is chronically debilitating and life-threatening due to blister formation in response to minor friction or trauma, leading to the development of multiple complications including life-threatening infections, failure to thrive, and predisposition to the development of squamous cell carcinoma.

The condition was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made.

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 genetically modified replication-incompetent herpes simplex virus-1 expressing collagen VII, for treatment of epidermolysis bullosa, was adopted by consensus.

2.1.12. - EMA/OD/233/17

Treatment of snakebite envenomation

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 26 February 2018, prior to responding to the list of issues.

2.1.13. Polatuzumab vedotin - EMA/OD/231/17

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

COMP coordinator: Lyubina Racheva Todorova

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

- Condition

The applicant acknowledges the recent evolution of the WHO classification with regards to the proposed orphan condition, but only appears to consider DLBCL-NOS subtype. The applicant is invited to justify this exclusion of other diffuse large B-cell lymphoma subtypes in the context of the updated guideline ENTR/6283/00 Rev 04 regarding a distinct medical entity valid for designation, or amend the condition to include all diffuse large B-cell lymphoma subtypes.

- Number of people affected

In light of the need to consider the proposed definition of the orphan condition, the applicant is requested to ensure that all diffuse large B-cell lymphoma subtypes are accounted for in the prevalence calculation. 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".

In the written response, the sponsor acknowledged the evolution in the WHO classification, and concurs with previous considerations of the COMP, discussing that the scope of this indication "would include all the subtypes mentioned in the EMA/COMP summary report including DLBCL-NOS (with two further subtypes of germinal center B-cell type and activated B-cell type), primary diffuse large B-cell lymphoma of the CNS, primary cutaneous diffuse large B-cell lymphoma, EBV+ DLBCL NOS, HHV8+ DLBCL NOS, diffuse large B-cell lymphoma associated with chronic inflammation, T-cell histiocytic rich large B cell lymphoma". The closely linked primary mediastinal (thymic) large B-cell lymphoma has been previously separately designated by the COMP and is not covered by this application. This was considered acceptable by the COMP.

With regards to the prevalence issue the estimate was revised upwards to 4.24 per 10,000 by using a) a 10-year period prevalence for 2017 NHL cases relying on IARC and NORDCAN databases and b) an assumption that 47.8% of NHL cases are diffuse large B-cell lymphoma, based on the Smith *et al*. (2015) analysis of the UK Hematologic Malignancy Research Network data.

The Committee agreed that the condition, diffuse large B-cell lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing polatuzumab vedotin was considered justified based on clinical observations supporting improved survival in relapsed/refractory patients when the proposed treatment is added on to other existing treatments.

The condition is chronically debilitating due to involvement of single or multiple nodal or extra nodal sites, including the gastrointestinal tract and bone marrow and life-threatening with 5-year survival rates reported as low as approximately 25% for high risk patients.

The condition was estimated to be affecting approximately 4.3 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 polatuzumab vedotin will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical and preliminarily clinical observations in relapsed/refractory patients supporting add-on effects in terms of clinical response and survival, when the product is combined with other existing treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for polatuzumab vedotin, for treatment of diffuse large B-cell lymphoma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/259/17

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 April meeting.

2.2.2. Adeno-associated viral vector serotype 8 containing the human acid alfa-glucosidase-gene - EMA/OD/255/17

Dr Philippe Moullier; Treatment of glycogen storage disease type II (Pompe's disease)

COMP coordinator: Fernando Hermida

The Committee agreed that the condition, glycogen storage disease type II (Pompe'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 adeno-associated viral vector serotype 8 containing the human acid alpha-glucosidase gene was considered justified based on non-clinical data which showed that there was a reduction in glycogen as well as an increased motor function.

The condition is chronically debilitating and life-threatening, in particular due to progressive weakness of muscles, respiratory and cardiac failure with limited survival.

The condition was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype 8 containing the human acid alpha-glucosidase gene will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical *in vivo* data that demonstrate a higher reduction in glycogen as well as an increased motor function when the product was used in combination with enzyme replacement therapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 8 containing the human acid alpha-glucosidase gene, for treatment of glycogen storage disease type II (Pompe's disease), was adopted by consensus.

2.2.3. Adeno-associated viral vector serotype 9 encoding miRNA against human superoxide dismutase 1 - EMA/OD/254/17

Stolmár & Partner Patentanwälte PartG mbB; Treatment of amyotrophic lateral sclerosis

COMP coordinator: Robert Nistico

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 9 encoding miRNA against human superoxide dismutase 1 was considered justified based on data in a valid *in vivo* model of the condition, supporting improvements in motor function.

The condition is life-threatening and chronically debilitating due to progressive degeneration of motor neurons, ultimately leading to paralysis and respiratory failure. Typically, death due to respiratory paralysis occurs in 3 to 5 years of the condition.

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 adeno-associated viral vector serotype 9 encoding miRNA against human superoxide dismutase 1 will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data in a valid *in vivo* model of the condition, supporting improvements in motor function. This compares favourably to the authorised products, which do not target these manifestations. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 9 encoding miRNA against human superoxide dismutase 1, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.4. - EMA/OD/260/17

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 April meeting.

2.2.5. Branaplam - EMA/OD/249/17

Novartis Europharm Limited; Treatment of spinal muscular atrophy

COMP coordinator: Ingeborg Barisic/Elizabeth Penninga

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

The intention to treat the condition with the medicinal product containing branaplam was considered justified based on non-clinical data which showed near normal body weight growth, active feeding and motor behaviours and preliminary clinical data showing improvements in feeding and reduced need for ventilatory support.

The condition is life-threatening and chronically debilitating due to muscle wasting, weakness, failure to thrive, pulmonary and orthopaedic complications.

The condition was estimated to be affecting approximately 0.7 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing branaplam will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical and preliminary clinical data that show an improvement in feeding, normalisation in weight gain and motor function in the non-clinical models, and in the clinical setting with an oral formulation versus nusinersen which is given intrathecally, an improvement in motor function as well as reduction in the need for assisted feeding and ventilation. The Committee considered that this constitutes a clinically relevant advantage and major contribution to patient care.

A positive opinion for branaplam, for treatment of spinal muscular atrophy, was adopted by consensus.

2.2.6. Burosumab - EMA/OD/026/17

Ultragenyx Germany GmbH; Treatment of phosphaturic mesenchymal tumour

COMP coordinator: Dinko Vitezic

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

The intention to treat the condition with the medicinal product containing burosumab was considered justified based on preliminary clinical data demonstrating that treatment increased serum phosphorus leading to improvements in fatigue and pain in patients affected by tumour-induced osteomalacia associated with the condition.

The condition is chronically debilitating due to severe osteomalacia and low bone density leading to severe symptoms of musculoskeletal pain, fractures, muscle weakness, fatigue, and difficulty with ambulation. In rare cases tumours can be malignant that may metastasise and cause death.

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

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 burosumab will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data to support significant benefit. Patients were affected by the condition and had tumour-induced osteomalacia that was not curable by surgical resection and was inadequately managed by the currently authorised products for rickets and osteomalacia. Treatment with the product increased serum phosphorus leading to improvements in fatigue and pain. The Committee considered

that this constitutes a clinically relevant advantage for patients affected by tumour-induced osteomalacia associated with the condition.

A positive opinion for burosumab, for treatment of phosphaturic mesenchymal tumour, was adopted by consensus.

2.2.7. - EMA/OD/196/17

Treatment of biliary tract 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 April meeting.

2.2.8. - EMA/OD/248/17

Treatment of Shiga-Toxin Producing Escherichia Coli Haemolytic Uremic Syndrome

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

2.2.9. - EMA/OD/252/17

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 April meeting.

2.2.10. - EMA/OD/223/17

Treatment of multiple myeloma

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

2.2.11. - EMA/OD/250/17

Treatment of invasive aspergillosis

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

2.2.12. - EMA/OD/251/17

Prevention of invasive aspergillosis

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

2.2.13. - EMA/OD/256/17

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 April 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 seventeen applications submitted.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of acute hepatic porphyria

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 oesophagitis

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 gastrointestinal stromal tumours

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 pulmonary arterial hypertension

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 partial deep dermal and full thickness burns

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 amyotrophic lateral sclerosis

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

3.1.7. -

Treatment of sickle cell disease

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

3.1.8. -

Treatment of soft tissue sarcoma

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

3.2. Finalised letters

3.2.1. -

Treatment of Niemann-Pick disease, type C

The finalised letter was circulated for information.

3.2.2. -

Treatment of mucopolysaccharidosis type I

The finalised letter was circulated for information.

3.2.3. -

Treatment of glioma

The finalised letter was circulated for information.

3.2.4. -

Treatment of paroxysmal nocturnal haemoglobinuria

The finalised letter was circulated for information.

3.2.5. -

Treatment of adenosine deaminase-deficient-severe combined immunodeficiency

The finalised letter was circulated for information.

3.2.6. -

Treatment of adrenoleukodystrophy

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of acute myeloid leukaemia

The new request was noted.

3.3.2. -

Treatment of pemphigusThe new request was noted.

3.3.3. -

Treatment of small cell lung cancer

The new request was noted.

3.3.4. -

Treatment of tuberous sclerosis

The new request was noted.

3.3.5. -

Treatment of acute sensorineural hearing loss (acute acoustic trauma, sudden deafness and surgery induced acoustic trauma)

The new request was noted.

3.3.6. -

Treatment of Cushing's syndrome

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. Rubraca - rucaparib - EMEA/H/C/004272, EMA/OD/085/12, EU/3/12/1049

Clovis Oncology UK Ltd; Treatment of ovarian cancer

[*Post-meeting note: The COMP adopted the opinion by written procedure following its March meeting and upon adoption of CHMP opinion.*]

4.2.2. - inotersen – EMEA/H/C/004782, EMA/OD/098/13, EU/3/14/1250

IONIS USA Ltd; Treatment of ATTR amyloidosis

The status of the procedure at CHMP was noted.

4.2.3. - 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 status of the procedure at CHMP was noted. A question addressed to the applicant has been adopted.

4.2.4. - vestronidase alfa – EMA/OD/127/11, EU/3/12/973, EMEA/H/C/004438

Ultragenyx Germany GmbH; Treatment of mucopolysaccharidosis type VII (Sly syndrome)

The status of the procedure at CHMP was noted.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for two applications.

4.5. Orphan Maintenance Reports

Documents were circulated in MMD.

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

5.1. After adoption of CHMP opinion

5.1.1. Bosulif - Bosutinib - Type II variation – EMEA/H/C/002373/II/0025/G, EMEA/OD/160/09, EU/3/10/762

Pfizer Limited; Treatment of chronic myeloid leukaemia

CHMP rapporteur: Harald Enzmann

The status of the procedure at CHMP was noted. The sponsor withdrew the orphan status with the European Commission, prior to a final COMP opinion.

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

5.1.2. Lynparza - Olaparib – Type II variation – EMEA/H/C/003726/X/0016/G, EMEA/OD/063/07, EU/3/07/501

AstraZeneca AB; Treatment of ovarian cancer

CHMP rapporteur: Alexandre Moreau; CHMP co-rapporteur: Bart Van der Schueren

The status of the procedure at CHMP was noted. The sponsor withdrew the orphan status with the European Commission, prior to the final COMP opinion.

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

5.2. Prior to adoption of CHMP opinion

None

5.3. Appeal

None

5.4. On-going procedures

COMP co-ordinators were appointed for two applications.

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP Strategic Review & Learning meeting, 26-28 March 2018, Amsterdam, The Netherlands

Document(s) tabled:
Invitation COMP Strategic Review and Learning Meeting 26-28 March 2018

7.1.2. Protocol Assistance Working Group (PAWG)

The working group on Protocol Assistance met on 13 March 2018.

7.1.3. Non-Clinical Working Group

The working group on Non–Clinical met on 14 March 2018.

7.1.4. Condition Working Group

The working group on Condition met on 15 March 2018.

7.1.5. Prevalence Working Group

The working group on Prevalence met on 14 March 2018.

7.1.6. Change to timing of Scientific Committee Chair and Vice-Chair elections

Change to timing of Scientific Committee Chair and Vice-Chair elections was presented.

Document tabled:
2018 03_Timing of chair elections_presentation to Committees

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. Recommendations on eligibility to PRIME – report from CHMP

Document was circulated in MMD.

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

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

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

DRAFT Agenda PCWP-HCPWP_17-18 April was circulated in MMD.

Draft PCWP/HCPWP Work Plan for 2018-2019 was adopted.

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. 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 13-15 March 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	
Ioannis Kkolos	Member	Cyprus	No interests declared	
Katerina Kopečková	Member	Czech Republic	No restrictions applicable to this meeting	
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	
Melinda Sobor	Member	Hungary	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Vacant	Member	Liechtenstein		

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Robert Nistico	Member	Malta	No interests declared	
Violeta Stoyanova-Beninska	Member	Netherlands	No interests declared	
Ingrid Wang	Member	Norway	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Olimpia Neagu	Member	Romania	No interests declared	
Eva Malikova	Member	Slovak Republic	No interests declared	
Martin Mozina	Member	Slovenia	No interests declared	
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:	5.1.2.
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Virginie Hivert	Expert - in person*		No restrictions applicable to this meeting	
	Patient expert - in person*			
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

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/