EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Inspections, Human Medicines Pharmacovigilance and Committees

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 14-16 February 2017

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

14 February 2017, 09:00-19:00, room 2F

15 February 2017, 09:00-19:00, room 2F

16 February 2017, 09:00-12:00, 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).

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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 14-16 February 2017 was adopted with amendments.

1.3. Adoption of the minutes

The minutes for 17-19 January 2017 were adopted with 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/285/16

Treatment of acute myeloid leukaemia

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

- Significant benefit

The arguments on significant benefit are based on the potential improved efficacy in the condition, in the context of one preclinical model using an apparently resistant cell line.

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

In the written response, and during an oral explanation before the Committee on 14 February 2017, the sponsor discussed further preclinical data where the proposed product was compared to an existing treatment combination that is part of the standard of care of acute myeloid leukaemia, showing a comparable effect of some doses of the proposed product to the standard of care.

The COMP considered that at this point in time the preclinical data support comparable effects versus authorised products and further data, as for example effects in preliminary clinical settings, would be required to assess either a clinically relevant advantage or a major contribution to patient care versus all authorised counterparts.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 15 February 2017, prior to final opinion.

2.1.2. Acetylleucine - EMA/OD/276/16

IntraBio Ltd; Treatment of Niemann-Pick disease

COMP coordinator: 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:

- Intention to treat

The sponsor is invited to further elaborate on the mechanism of action of acetylleucine in Niemann-Pick type C, and on whether the product could be used in other forms of Niemann-Pick disease.

Further, to establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of Niemann-Pick disease type C, the sponsor should further elaborate on the ongoing compassionate use study, and in particular on:

- the exact number and location of patients, as it appears that this study is conducted in patients from Germany and Slovakia; however, 5 patients from the Czech Republic are also mentioned;

- how many of the patients of this study were enrolled in the previous studies, and which data are available from these patients;

- the results of patients in this study that have been treated with the proposed product for more than one year;

The sponsor is also invited to present any figure related to clinical responses in this study.

In addition the sponsor is invited to discuss the relevance of data in patients affected by cerebellar ataxia from different causes to the intended clinical use in Niemann-Pick (type C) disease.

- Significant benefit

The sponsor is invited to further discuss any claim of significant benefit and to substantiate such claims with any available preclinical and/or clinical data. It is to be noted that since a benefit/risk assessment of the proposed product has not been carried out, generic claims of a better benefit/risk profile do not appear substantiated at the present stage.

Furthermore, it would be useful to obtain more information on the ongoing planned clinical development of the product, and in particular whether development in forms of Niemann-Pick disease other than type C is envisioned.

In the written response, and during an oral explanation before the Committee on 14 February 2017, the sponsor further discussed the preclinical and clinical data supporting the medical plausibility and the significant benefit of the proposed product, showing improvement of function in preclinical models of the disease, as well as clinical and quality of life improvement in patients' testimonies. It was also clarified that based on the mechanism of action the product could potentially be used also in other forms of Niemann Pick disease other than type C.

Following review of the application by the Committee, it was agreed to broaden/rename the indication to treatment of Niemann-Pick disease.

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

The intention to treat the condition with the medicinal product containing acetylleucine was considered justified based on preclinical and preliminary clinical data showing improvement of ataxia symptoms.

The condition is chronically debilitating and life-threatening in particular due to complications such as neurological degeneration, splenomegaly, and hepatomegaly. The majority of patients with Niemann-Pick disease type A die before two years of age, while patients with other forms usually die in their twenties.

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

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 acetylleucine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing improvement of ataxia symptoms in patients affected by Niemann-Pick disease who were not adequately controlled with the currently authorized treatment. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for acetylleucine, for treatment of Niemann-Pick disease, was adopted by consensus.

2.1.3. - EMA/OD/217/16

Treatment of cystic fibrosis

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

- 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 cystic fibrosis, the sponsor should further elaborate on:

– the relevance of the preclinical antifungal outcome for patients with CF. In this context, please provide a scientific discussion on the link between lung deterioration and Aspergillus persistence and infection.

– the validity of the used preclinical model of invasive aspergillosis for testing the product for the treatment of cystic fibrosis

– the results obtained in the preclinical model. Please discuss the effect sizes and the heterogeneous outcomes, and please clarify any statistically significant differences relevant for assessment.

- Number of people affected

For the calculation and presentation of the prevalence estimate it 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.

- Significant benefit

The sponsor should provide an updated review of all authorised products in cystic fibrosis.

The arguments on significant benefit versus other authorised antifungal therapies are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor is requested to provide evidence to further support the theoretical arguments provided for significant benefit.

In the written response, and during an oral explanation before the Committee on 14 February 2017, the sponsor acknowledged the COMP concern that there is currently no evidence for a direct link between lung deterioration and aspergillus infection. The sponsor argued however that the carriage of non-lethal Aspergillus spp and other fungi can preclude patients from lung transplantation, which impacts adequate management of cystic fibrosis patients. Invasive aspergillosis does not generally occur in cystic fibrosis patients, unless they are otherwise immunocompromised. The COMP considered that while the preclinical models and outcomes subject of the submission were relevant for the condition of aspergillosis, the application did not provide adequate evidence in relevant preclinical models to support medical plausibility for the treatment of cystic fibrosis.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 February 2017, prior to final opinion.

2.1.4. - EMA/OD/219/16

Treatment of invasive aspergillosis

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

Invasive aspergillosis should be justified as a distinct medical entity or a valid subset of aspergillosis. Note that this is for the purposes of orphan medicinal product designation; the

sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00). The argumentation is expected to be based on pathophysiology, histopathology, clinical characteristics and classification systems.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of invasive aspergillosis, the sponsor should further elaborate on the results obtained in the preclinical model. Please discuss the effect sizes and the heterogeneous outcomes, and please clarify any statistically significant differences relevant for assessment.

In the written response, and during an oral explanation before the Committee on 14 February 2017, the sponsor provided new preclinical data and acknowledged the heterogeneity of the study outcomes, which did not show statistically significant improvements in tissue burden and survival. In this context, the sponsor explained that the disease model has not yet been fully optimised to study the type of product and therefore a trend of improvement was a relevant outcome. Nevertheless, the COMP determined that the presented data was inconclusive and therefore concluded that additional evidence would be necessary to fully clarify medical plausibility of the proposed product.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 February 2017, prior to final opinion.

2.1.5. - EMA/OD/262/16

Treatment of pancreatic 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:

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor submitted in vitro data which are considered too preliminary by the COMP to be able to establish the basis of significant benefit. In the absence of pre-clinical in vivo or preliminary clinical data from the sponsor, the COMP cannot establish significant benefit. The sponsor is therefore invited to present additional pre-clinical in vivo or preliminary clinical data in the condition to establish significant benefit. This should be discussed within the context of the authorised medicines where gemcitabine and nab-paclitaxel are used for the treatment of the condition in the European Union.

In the written response, and during an oral explanation before the Committee on 14 February 2017, the sponsor provided some additional data showing the combined effect of their product with gemcitabine in a model of the condition, showing that when their product was used in combination with the gemcitabine the combined effect was superior to gemcitabine on its own or the sponsor's product used alone. The most up to date ESMO Guidelines indicate that the patients will receive gemcitabine in the following combination nab+paclitaxel+gemcitabine, therefore the COMP would need to see data where the proposed product would show a clinically relevant advantage with respect to the use of nab+paclitaxel+gemcitabine, in order to grant significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 February 2017, prior to final opinion.

2.1.6. - EMA/OD/227/16

Treatment of epidermolysis bullosa

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 epidermolysis bullosa, the sponsor should further elaborate on the studies performed in the cited preclinical model with regards to the absence of untreated control in the experiments performed.

In the written response, and during an oral explanation before the Committee on 14 February 2017, the sponsor provided raw data for the figures presented, as well as some further data, again with controls from previous experiment rather than concurrent controls. Moreover, the scoring data of the historical controls provided by the sponsor were not complete, and as such it was not possible to understand the variability of the observations.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 February 2017, prior to final opinion.

2.1.7. Cannabidiol - EMA/OD/275/16

GW Research Ltd; Treatment of Lennox-Gastaut syndrome

COMP coordinator: Giuseppe Capovilla/Dinah Duarte

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

In the application, the sponsor has provided data on the changes that the administration of the product induces in drop seizures and overall seizures frequency. No source data were available for evaluation and no data to support the mechanism of action or preclinical efficacy was presented.

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

- the results obtained in vitro and in vivo in support of the mechanism of action and pharmacology of the product,
- the original data from both Phase 3 clinical trials, including detailed information on the types of drop seizures measured,
- EEG picture, in particular the therapeutic effect of the product on atypical absences and slow spike and wave discharges,

- the pharmacokinetic interactions of cannabidiol with co-administered products, in particular in context of the published information about the elevation of levels of clobazam metabolites following the administration of cannabidiol.

- Number of people affected

For the calculation and presentation of the prevalence estimate it 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 re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition and to 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.

- Significant benefit

The sponsor claims significant benefit based on improved efficacy when the product is used on top of the standard of care or in patients failing to respond to lamotrigine, topiramide and rufinamide. No discussion was provided to compare the efficacy of felbamate and cannabidiol. The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. Yet, the mechanism of action of the product was not clearly presented and the concomitant treatment of the studied population has not been listed.

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

The sponsor should detail the results of any clinical data they have 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 15 February 2017, the sponsor presented detailed study reports from non-clinical and clinical studies performed to date. In addition the sponsor provided amended prevalence calculation which was accepted by the committee. With regards to the significant benefit, the sponsor presented additional data demonstrating that cannabidiol induced significant responses also in patients who were not adequately managed using some of the currently authorized products.

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

The intention to treat the condition with the medicinal product containing cannabidiol was considered justified based on clinical data demonstrating reduced seizure frequency in patients who received the product on top of standard of care.

The condition is chronically debilitating due to the high frequency of multiple types of seizures, cognitive deterioration, behavioural disturbances, and poor long term prognosis despite existing treatments.

The condition was estimated to be affecting approximately 2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing cannabidiol will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who failed to respond to authorised products achieved a reduction of seizure frequency. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for cannabidiol, for treatment of Lennox-Gastaut syndrome, was adopted by consensus.

2.1.8. - EMA/OD/261/16

Treatment of idiopathic pulmonary fibrosis

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

- 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 idiopathic pulmonary fibrosis, the sponsor is invited to further discuss the results of the preclinical capsaicin-induced cough study, and in particular:

– the grounds on which a specific activity of the product on IPF-related cough is assumed, taking into account the low number of cough episodes in the naïve group, and the lower magnitude of effect as compared to codeine shown on cough after bleomycin challenge;

– the relevance of the preclinical data, showing approximately 50% reduction of cough episodes but controversial effects on fibrosis, to the intended clinical use in idiopathic pulmonary fibrosis

– whether the therapeutic target is cough or fibrosis. In relation to this, the sponsor is invited to present any other available preclinical and/or clinical data supporting the anti-fibrotic effects of the product in relevant IPF models;

- Number of people affected

The sponsor is invited to present a final figure of affected population in 10,000 in the EU, and to discuss the way such figure is calculated. The sponsor is reminded that prevalence calculations should be based on a wide range of sources, including literature and registries, whenever possible, and that critical appraisal of the sources is needed.

- Significant benefit

The sponsor is invited to support any claim of better efficacy of the proposed product with comparative discussion in relation to the currently authorized products for the treatment of IPF. In addition, since the product appears to be targeting mainly cough, the sponsor is invited to discuss significant benefit in relation to the existing symptomatic treatments for cough used in IPF.

Claims of significant benefit should be supported by relevant preclinical and/or clinical evidence in the proposed condition.

In the written response, and during an oral explanation before the Committee on 15 February 2017, the sponsor further discussed the data relative to the anti-fibrotic activity and the antitussive activity of the proposed product. The COMP noted that the data supporting the anti-fibrotic efficacy were not conclusive, based on the methodology of some of the preclinical experiments and the controversial results. The COMP was of the opinion that the medical plausibility could not be justified only by the antitussive effects of the product in absence of a clear anti-fibrotic effect.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 February 2017, prior to final opinion.

2.1.9. Inebilizumab - EMA/OD/267/16

AstraZeneca AB; Treatment of Neuromyelitis Optica Spectrum Disorders (NMOSD)

COMP coordinator: Michel Hoffmann

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 neuromyelitis optica spectrum disorders (NMOSD), the sponsor should further elaborate on:

– the relevance of the preclinical model used for the treatment of NMOSD, and the interpretation of the results obtained in the experiment,

– the availability of any preliminary clinical data from an on-going study with the product in patients with the condition.

In the written response, the sponsor submitted additional data from a very recent publication, showing a superior effect in the depletion of the majority of tissue B cells and autoantibody-producing plasma cells, reduction in pathogenic autoantibody titers, a suppression of autoimmune CNS inflammation and prevention of disease onset and exacerbation when compared to CD20 monoclonal antibody. The COMP accepted that this additional data addressed the concerns raised in the list of questions. The COMP also accepted the sponsor's claim that they could not present any clinical data as the trial was still on-going and unblinding it could compromise the results.

The Committee agreed that the condition, neuromyelitis optica spectrum disorders, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing inebilizumab was considered justified based on pre-clinical in vivo data showing a depletion in the majority of tissue B cells and autoantibody-producing plasma cells, a reduction in pathogenic autoantibody titers, and a suppression of autoimmune CNS inflammation.

The condition is chronically debilitating and life-threatening due to neurological impairment such as paraplegia, sensory loss, bladder dysfunction, peripheral pain, and increased 5-year mortality.

The condition was estimated to be affecting approximately 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for inebilizumab, for treatment of neuromyelitis optica spectrum disorders, was adopted by consensus.

2.1.10. Antisense oligonucleotide targeting the *USH2A* gene - EMA/OD/280/16

ProQR Therapeutics IV BV; Treatment of retinitis pigmentosa

COMP coordinator: Armando Magrelli

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

- 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 RP, the sponsor should further elaborate on:

The relevance of the preclinical model used for the treatment of RP, and the interpretation of the results obtained in the experiment. This should be discussed particularly in view of the availability of other pre-clinical models used for this condition and in particular as it has been noted that transgenic models which are designed with the specific mutation which the sponsor is targeting are publically available.

In the written response, the sponsor provided compelling arguments that the development of a preclinical model of the condition would be very difficult to achieve due to the mode of action of the product. The COMP considered that due to the uniqueness of the mode of action the use of the currently available models of this specific mutation in retinitis pigmentosa would make it difficult to establish the effectiveness of the product in the condition. In view of these limitations the COMP accepted the data generated in the model presented by the sponsor for this specific situation.

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

The intention to treat the condition with the medicinal product containing antisense oligonucleotide targeting the USH2A gene was considered justified based on preliminary pre-clinical in vivo data which showed an improvement of retinal function as shown through a recovery of the electroretinogram amplitude.

The condition is chronically debilitating due to the development of nyctalopia and tunnel vision that progresses to total blindness.

The condition was estimated to be affecting approximately 2.9 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for antisense oligonucleotide targeting the *USH2A* gene, for treatment of retinitis pigmentosa, was adopted by consensus.

2.1.11. - EMA/OD/289/16

Treatment of cystic fibrosis

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 30 January 2017, prior to responding to the list of issues.

2.1.12. - EMA/OD/255/16

Treatment of pancreatic 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:

- Significant benefit

In order to justify the significant benefit of the proposed product the sponsor is invited to present a comparative discussion *vis a vis* the currently authorised treatments for pancreatic cancer. Any claim of significant benefit should be supported by relevant preclinical and/or clinical data.

In the written response, and during an oral explanation before the Committee on 15 February 2017, the sponsor further discussed preclinical experiments suggested beneficial effects by blocking metastatic biochemical pathways and reversing the immune surveillance disorder of the cancer. However no proof of concept data supporting the significant benefit in relation to the authorized treatments were available, therefore the COMP was of the opinion that there were not sufficient data to establish the significant benefit of the proposed product 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 16 February 2017, prior to final opinion.

2.1.13. - EMA/OD/278/16

Treatment of short bowel 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 27 January 2017, prior to responding to the list of issues.

2.1.14. - EMA/OD/266/16

Treatment of pancreatic 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:

- 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 pancreatic cancer, the sponsor should further elaborate on:

– the relevance of the preclinical model used for the treatment of pancreatic cancer, and the interpretation of the results obtained in the experiments

– the preliminary clinical data discussed, in particular with regards to any dose-response effects of the proposed product and why the effects observed can be attributed to the study product and not to concomitant first line chemotherapy.

- Number of people affected

For the calculation and presentation of the prevalence estimate it 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 is invited to perform the exercise using crude and not age-adjusted incidence.

- Significant benefit

The arguments on significant benefit are based on the potential combination with authorised products. The sponsor is invited to further discuss the arguments provided for significant benefit and to elaborate on the results from the preliminary clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. The comparability of the populations and results of any historical comparators used should be discussed in detail.

In the written response, and during an oral explanation before the Committee on 16 February 2017, the sponsor elaborated further with regards to the clinical observations of the phase 1 study. It was argued that efficacy parameters were "usually better or comparable" than in literature, but figures of these comparisons were not available.

As regards the prevalence issue, the applicant also further discussed the increasing incidence of the condition and provided a figure for both US and EU.

The COMP considered that the effects of the product in the preliminary clinical study were difficult to understand given the add-on settings and uncontrolled nature of the observations. Moreover, there was no clear dose response in the cohorts studied, and a comparative discussion versus the expected effects of the baseline chemotherapy alone was missing. This would preclude a justification of a clinically relevant advantage or major contribution to patient care versus the authorised products.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 February 2017, prior to final opinion.

2.1.15. - EMA/OD/288/16

Treatment of short bowel 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 31 January 2017, prior to responding to the list of issues.

2.1.16. - EMA/OD/284/16

Treatment of amyotrophic lateral sclerosis

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 31 January 2017, prior to responding to the list of issues.

2.1.17. Ketoconazole - EMA/OD/234/16

Grupo Español de Tumores Huérfanos e Infrecuentes (GETHI); Treatment of granulosa cell tumours

COMP coordinator: Bożenna Dembowska-Bagińska

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

- Number of people affected

The sponsor provided a calculation of annual incidence of granulosa cell tumours. Instead, the sponsor is requested to provide an estimate of point prevalence, taking into account the incidence of GCTs in both sexes and the current life expectancy of patients with granulosa cell tumours.

For the calculation and presentation of the prevalence estimate it 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 provided an estimate of the prevalence of granulosa cell tumours (GCT) taking into consideration reported incidence data and published estimates of disease duration. The estimate was considered acceptable and the proposed value of 0.12 was rounded up to 0.2 in 10,000 persons in the EU to account for an unknown number of rare cases that occur in males and children.

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

The intention to treat the condition with the medicinal product containing ketoconazole was considered justified based on early clinical data in patients with refractory and recurrent disease who achieved a long term stabilisation of the disease.

The condition is life-threatening due to disease progression and metastasis and chronically debilitating due to abdominal or pelvic pain, nausea, vomiting and dizziness.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing ketoconazole will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who relapsed after all available treatment options responded to treatment with the product in combination with the standard of care and achieved a long term stabilisation

of the disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for ketoconazole, for treatment of granulosa cell tumours, was adopted by consensus.

2.1.18. Megestrol acetate - EMA/OD/236/16

Grupo Español de Tumores Huérfanos e Infrecuentes (GETHI); Treatment of granulosa cell tumours

COMP coordinator: Bożenna Dembowska-Bagińska

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

- Number of people affected

The sponsor provided a calculation of annual incidence of granulosa cell tumours. Instead, the sponsor is requested to provide an estimate of point prevalence, taking into account the incidence of GCTs in both sexes and the current life expectancy of patients with granulosa cell tumours.

For the calculation and presentation of the prevalence estimate it 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 provided an estimate of the prevalence of granulosa cell tumours (GCT), taking into consideration reported incidence data and published estimates of disease duration. The estimate was considered acceptable and the proposed value of 0.12 was rounded up to 0.2 in 10,000 persons in the EU to account for an unknown number of rare cases that occur in males and children.

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

The intention to treat the condition with the medicinal product containing megestrol acetate was considered justified based on early clinical data in patients with refractory and recurrent disease who achieved partial and full responses.

The condition is life-threatening due to disease progression and metastasis and chronically debilitating due to abdominal or pelvic pain, nausea, vomiting and dizziness.

The condition was estimated to be affecting approximately 0.2 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing megestrol acetate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients who relapsed after all available treatment options responded to treatment with the product and achieved partial or complete responses. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for megestrol acetate, for treatment of granulosa cell tumours, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate - EMA/OD/201/16

Daiichi Sankyo Europe GmbH; Treatment of soft tissue sarcoma

COMP coordinator: Frauke Naumann-Winter/Katerina Kopečková

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

The intention to treat the condition with the medicinal product containing (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate was considered justified based on preliminary clinical data which showed that patients with liposarcoma had a better progression free survival than historical controls.

The condition is chronically debilitating with a high recurrence and metastasis rate, and life-threatening with an overall 5-year survival rate of approximately 60%.

The condition was estimated to be affecting approximately 3.3 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate a substantially improved progression free survival in relapsed refractory liposarcoma patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (3'R,4'S,5'R)-N-[(3R,6S)-6-carbamoyltetrahydro-2H-pyran-3-yl]-6''-chloro-4'-(2-chloro-3-fluoropyridin-4-yl)-4,4-dimethyl-2''-oxo-1'',2''-dihydrodispiro[cyclohexane-1,2'-pyrrolidine-3',3''-indole]-5'-carboxamide mono(4-methylbenzenesulfonate) monohydrate, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2.2. - EMA/OD/308/16

Treatment of acromegaly

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 March meeting.

2.2.3. - EMA/OD/314/16

Treatment of ovarian cancer

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

2.2.4. - EMA/OD/299/16

Treatment of pulmonary arterial hypertension

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

2.2.5. Adeno-associated viral vector serotype 8 containing the human alpha-galactosidase A gene - EMA/OD/277/16

Freeline Therapeutics Ltd; Treatment of Fabry disease

COMP coordinator: Pauline Evers

Following review of the application by the Committee, it was agreed to broaden/rename the active substance to adeno-associated viral vector serotype 8 containing the human alpha-galactosidase A gene.

The Committee agreed that the condition, 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 adeno-associated viral vector serotype 8 containing the human alpha-galactosidase A gene was considered justified based on an in vivo model of the condition, supporting that a single administration of the product results in sustained increase of galactosidase activity.

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 people 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 viral vector serotype 8 containing the human alpha-galactosidase A gene will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that a single administration of the product results in a long-term sustained increase of a-galactosidase activity, which would obviate the need for regular treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 8 containing the human alpha-galactosidase A gene, for treatment of Fabry disease, was adopted by consensus.

2.2.6. Adeno-associated viral vector serotype LK03 encoding human ornithine transcarbamylase - EMA/OD/310/16

Dr Julien Baruteau; Treatment of ornithine transcarbamylase deficiency

COMP coordinator: Irena Bradinova/Armando Magrelli

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype LK03 encoding human ornithine transcarbamylase was considered justified based on preclinical data showing reduction of orotic aciduria, a relevant biomarker of the disease.

The condition is life-threatening and chronically debilitating due to repeated metabolic decompensation with hyperammonaemia, leading to neurological damage with developmental delay, mental disability, coma, seizures and respiratory arrest.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype LK03 encoding human ornithine transcarbamylase will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing reduction of markers of disease with the proposed treatment, with a mechanism of action that has a disease-modifying potential. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for adeno-associated viral vector serotype LK03 encoding human ornithine transcarbamylase, for treatment of ornithine transcarbamylase deficiency, was adopted by consensus.

2.2.7. Adeno-associated virus (AAV) serotype rh.10 expressing ß-galactosidase - EMA/OD/265/16

LYSOGENE; Treatment of GM1 gangliosidosis

COMP coordinator: Lesley Greene/Armando Magrelli

The Committee agreed that the condition, GM1 gangliosidosis, 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 rh.10 expressing beta-galactosidase was considered justified based on pre-clinical in vivo data showing an improvement in beta-galactosidase activity in valid models of the condition.

The condition is life-threatening due to a reduced life expectancy in the moderate to severe forms of the condition which make up 90% of those affected and chronically debilitating due to neurodegeneration associated with seizures, hepatomegaly, splenomegaly, skeletal irregularities, joint stiffness, muscle weakness and problems with gait.

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

The sponsor has also established that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition/for the population at risk of developing the condition.

A positive opinion for adeno-associated viral vector serotype rh.10 expressing beta-galactosidase, for treatment of GM1 gangliosidosis, was adopted by consensus.

2.2.8. Allogeneic, ex vivo expanded, umbilical cord blood-derived, hematopoietic CD34+ progenitor cells and allogeneic, non-expanded, umbilical cord blood-derived, hematopoietic mature myeloid and lymphoid cells - EMA/OD/257/16

Regulatory Resources Group Ltd; Treatment in haematopoietic stem cell transplantation

COMP coordinator: Frauke Naumann-Winter/Karri Penttila

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

The intention to treat the condition with the medicinal product containing allogeneic ex-vivo-expanded umbilical cord blood-derived hematopoietic CD34+ progenitor cells and allogeneic non-expanded umbilical cord blood-derived hematopoietic mature myeloid and lymphoid cells was considered justified based on preliminary clinical data confirming engraftment of haemopoietic progenitor cells in patients subjected to haematopoietic stem cell transplantation.

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

The condition was estimated to be 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic ex-vivo-expanded umbilical cord blood-derived hematopoietic CD34+ progenitor cells and allogeneic non-expanded umbilical cord blood-derived hematopoietic mature myeloid and lymphoid cells will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data confirming engraftment of haemopoietic progenitor cells in patients subjected to haematopoietic stem cell transplantation. The authorised products are used in the treatment of different aspects of the procedure. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic ex-vivo-expanded umbilical cord blood-derived hematopoietic CD34+ progenitor cells and allogeneic non-expanded umbilical cord blood-derived hematopoietic mature myeloid and lymphoid cells, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.2.9. - EMA/OD/302/16

Treatment of epidermolysis bullosa due to mutations in the *COL7A1* gene

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 March meeting.

2.2.10. Autologous adipose tissue-derived mesenchymal stem cells - EMA/OD/204/16

SPC GmbH; Treatment of thromboangiitis obliterans (Buerger's disease)

COMP coordinator: Violeta Stoyanova

The Committee agreed that the condition, thromboangiitis obliterans (Buerger'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 autologous adipose tissue-derived mesenchymal stem cells was considered justified based on preliminary clinical data in patients with the condition showing an improvement in the pain free walking distance.

The condition is chronically debilitating due to the development of ulcers, gangrene and risk of amputation.

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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous adipose tissue-derived mesenchymal stem cells will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients not eligible for surgery could walk for a greater distance when treated with the sponsor's product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous adipose tissue-derived mesenchymal stem cells, for treatment of thromboangiitis obliterans (Buerger's disease), was adopted by consensus.

2.2.11. - EMA/OD/313/16

Treatment of Asherman's 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 March meeting.

2.2.12. - EMA/OD/270/16

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 March meeting.

2.2.13. - EMA/OD/315/16

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 March meeting.

2.2.14. - EMA/OD/309/16

Treatment of neonatal encephalopathy

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 March meeting.

2.2.15. - EMA/OD/287/16

Treatment of graft rejection following solid organ transplantation

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 March meeting.

2.2.16. - EMA/OD/301/16

Treatment of narcolepsy

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 March meeting.

2.2.17. - EMA/OD/294/16

Treatment of calciphylaxis

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 March meeting.

2.2.18. - EMA/OD/293/16

Treatment of fragile X 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 March meeting.

2.2.19. Phosphoinositide 3-kinase gamma peptide - EMA/OD/303/16

Kither Biotech s.r.l.; Treatment of cystic fibrosis

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing phosphoinositide 3-kinase gamma peptide was considered justified based on preclinical data demonstrating a potentiation effect on cystic fibrosis transmembrane conductance regulator (CFTR) proteins when used chronically in combination with an authorised product.

The condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing phosphoinositide 3-kinase gamma peptide will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the product can be used chronically without losing its potentiation effects on CFTR proteins. In addition, the product could be used in combination with the standard of care. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for phosphoinositide 3-kinase gamma peptide, for treatment of cystic fibrosis, was adopted by consensus.

2.2.20. Poly-cyclodextrin-bis-cysteine-PEG3400-camptothecin-conjugate - EMA/OD/300/16

Viadoc Business Solutions Limited; Treatment of ovarian cancer

COMP coordinator: Brigitte Bloechl-Daum

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 poly-cyclodextrin-bis-cysteine-PEG_{3400}-camptothecin-conjugate was considered justified based on early clinical data demonstrating achievement of partial responses in patients suffering from platinum-resistant advanced ovarian cancer when the product was used on top of standard of care.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing poly-cyclodextrin-bis-cysteine-PEG_{3400}-camptothecin-conjugate will be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that patients with platinum-resistant advanced ovarian cancer, who received treatment in combination with the standard of care or who relapsed while treated with authorised second line products, achieved partial responses. In addition, the sponsor demonstrated synergistic effects of the product when used in combination with available second line therapies for platinum-resistant ovarian cancer. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for poly-cyclodextrin-bis-cysteine-PEG_{3400}-camptothecin-conjugate, for treatment of ovarian cancer, was adopted by consensus.

2.2.21. - EMA/OD/286/16

Treatment of graft rejection following solid organ transplantation

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 March meeting.

2.2.22. - EMA/OD/253/16

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 March meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

2.5.1. 20% I.V. fat emulsion consisting of 20% soybean oil, 1.2% egg yolk phospholipids, 2.25% glycerin, and water for injection - EMA/OD/062/16

Alan Boyd Consultants Ltd; Treatment of poisoning by local anesthetics

COMP coordinators were appointed.

Documents tabled:
Grounds for appeal

Notes:
Appeal of the negative COMP opinion adopted in November 2016.

2.6. Nominations

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

COMP coordinators were appointed for 16 applications submitted.

Document tabled:
OMPD applications - appointment of coord. at the 14-16 February 2017 COMP meeting

2.7. Evaluation on-going

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

Notes:
See 7.8.1. Table 6. Evaluation Ongoing.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of Gaucher disease

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

3.1.2. -

Treatment of amyotrophic lateral sclerosis

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 narcolepsy

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

3.1.4. -

Treatment of Langerhans cell histiocytosis

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

3.1.5. -

Treatment of glioma

The COMP was informed that no significant benefit questions were identified

3.1.6. -

Treatment of Wolfram syndrome

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

3.1.7. -

Treatment of Wolfram syndrome

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

3.2. Finalised letters

3.2.1. -

Treatment of paroxysmal nocturnal haemoglobinuria

The finalised letter was circulated for information.

3.2.2. -

Treatment of autosomal dominant polycystic kidney disease

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of paroxysmal nocturnal haemoglobinuria

The new request was noted.

4. Review of orphan designation for orphan medicinal products for 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. - cerliponase alfa - EMA/OD/177/12, EU/3/13/1118, EMEA/H/C/004065

BioMarin International Limited; Treatment of neuronal ceroid lipofuscinosis type 2

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to respond in writing before the Committee at the March meeting.

4.2.2. Natpar - parathyroid hormone – EMA/OD/102/13, EU/3/13/1210, EMEA/H/C/003861

NPS Pharma Holdings Limited; Treatment of hypoparathyroidism

COMP coordinator: Vallo Tillmann

The COMP concluded that:

The proposed therapeutic indication, the long-term treatment of adult patients with hypoparathyroidism falls entirely within the scope of the orphan indication of the designated orphan medicinal product, treatment of hypoparathyroidism.

The proposed therapeutic indication “adjunctive treatment of adult patients with chronic hypoparathyroidism who cannot be adequately controlled with standard therapy alone” falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of hypoparathyroidism (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be 3.5 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening and chronically debilitating due to neuromuscular symptoms, cognitive impairment, abnormal calcium and phosphate metabolism, and reduced bone turnover. The condition may be life-threatening due to risk of hypocalcaemia that may lead to seizures, cardiac arrhythmias, cardiomyopathy and laryngeal spasm if untreated.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Natpar may be of potential significant benefit to those affected by the orphan condition. This is based on clinical data showing maintenance of normal calcium serum levels, reducing the need of the administration of calcium and vitamin D supplements treatment. The COMP considered that this constitutes a clinically relevant advantage for the patients affected by hypoparathyroidism.

An opinion not recommending the removal of Natpar (recombinant human parathyroid hormone, parathyroid hormone)(EU/3/13/1210) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

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

4.2.3. - pentosan polysulfate sodium – EMA/OD/179/14, EU/3/14/1411, EMEA/H/C/004246

Bene-Arzneimittel GmbH; Treatment of interstitial cystitis

The COMP noted that the oral explanation at COMP will be postponed to March 2017.

4.3. Appeal

None

4.4. On-going procedures

COMP co-ordinators were appointed for 2 applications.

4.5. Public Summary of Opinions

The draft public summaries of the COMP opinions adopted last month were endorsed for publication on the EMA website.

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

None

5.3. Appeal

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. Protocol Assistance Working Group

The working group on Protocol Assistance met on 14 February 2017.

7.1.2. COMP Strategy Review & Learning meetings, 19-20 March 2016, Valletta, Malta

Draft agenda was discussed.

7.1.3. Survey to Committee members, alternates and concerned NCA staff on the service and support provided by EMA Committee Secretariats - Findings

A short survey was sent in 2016 to all Committee members on the quality of the service offered. Overall there was a good satisfaction level for the work of the secretariats.

7.1.4. Selection procedure for COMP members nominated by the EC on EMA recommendation

The COMP was informed that a selection procedure for COMP members nominated by the EC was on-going.

7.1.5. COMP Membership

The COMP welcomed Ioannis Kkolos as new member representing Cyprus.

The COMP welcomed Lyubina Racheva Todorova as new member representing Bulgaria.

7.2. Coordination with EMA Scientific Committees or CMDh-v

7.2.1. PDCO/COMP Working Group

The PDCO/COMP working group took place on 15 February 2017 by teleconference.

7.2.2. Recommendations on eligibility to PRIME – report from CHMP

Documents were circulated in MMD.

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

None

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

The draft agenda of the monthly teleconference with FDA held on 24 January 2017 is available in MMD for information.

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

7.7.1. COMP Work Plan 2017

The updated COMP Work Plan 2017 was circulated for information.

7.8. Planning and reporting

7.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2017 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. -

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 14-16 February 2017 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 *via TC*	Austria	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 restrictions applicable to this meeting	
Katerina Kopeckova	Member	Czech Republic	No restrictions applicable to this meeting	
Jens Ersbøll	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	
Sigurdur B. Thorsteinsson	Member	Iceland	No interests declared	
Armando Magrelli	Member *via TC*	Italy	No interests declared	
Geraldine O'Dea	Member	Ireland	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	

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	
Dan Henrohn	Member	Sweden	No restrictions applicable to this meeting	
Daniel O'Connor	Member	United Kingdom	No interests declared	
Lesley Greene	Member (Vice-Chair)	Patients' Organisation Representative	No interests declared	
Kerstin Westermark	Member	Expert recommended by EMA	No participation in final deliberations and voting on:	2.1.9.
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Liam Galvin	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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

Explanatory notes

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

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use
COMP: Committee for Orphan Medicinal Products
EC: European Commission
OD: Orphan Designation
PA: Protocol Assistance
PDCO: Paediatric Committee
PRAC: Pharmacovigilance and Risk Assessment Committee
SA: Scientific Advice
SAWP: Scientific Advice Working Party

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

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

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

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

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

Sponsor

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

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

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

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