15 February 2018
EMA/COMP/31472/2018
Inspections, Human Medicines Pharmacovigilance and Committees

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 16-18 January 2018

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

16 January 2018, 08:30-19:30, room 2F

17 January 2018, 08:30-19:30, room 2F

18 January 2018, 08:30-14:00, 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 16-18 January 2018 was adopted with no amendments.

1.3. Adoption of the minutes

The minutes for 05-07 December 2017 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/188/17

Treatment of chronic 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:

- 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 chronic myeloid leukaemia, the sponsor should further elaborate on:

  - the orthotopic *in vivo* models of CML study by reviewing the accuracy of the figures provided in the application and by providing more information on the study.

- Significant benefit

The sponsor attempts to argue significant benefit of the product in the T315I mutation patient population in terms of comparable efficacy and better safety against ponatinib, an authorised TKI for use in this patient population.

It is well known that extrapolation from non-clinical or early clinical studies cannot fully predict the safety of a product in its clinical setting, thus other relevant data is required to justify safety arguments in most cases.

The sponsor should clearly position the product within current treatment algorithms of CML and identify a subgroup of patients where data driven significant benefit against currently authorised treatment modalities in terms of either a clinically relevant advantage or a major contribution to patient care can be demonstrated. Of special interest is further elaboration on whether any of the patients in the clinical trial were pretreated with ponatinib.

In the written response, and during an oral explanation before the Committee on 16 January 2018, the sponsor further elaborated on the results of the *in vivo* models by providing individual survival data. The COMP considered the additional data provided as adequate to support the medical plausibility. With regard to significant benefit, the sponsor provided additional data from non-clinical studies and the clinical trial. The COMP questioned the extrapolation from non-clinical and preliminary clinical data of the safety profile of the proposed product and thus the validity of its comparison with the authorised ponatinib on safety grounds. The sponsor also provided additional data on two patients from the phase I trial who were pretreated with ponatinib. The COMP considered that the currently available data are not sufficient to substantiate the significant benefit of the product against authorised products for the condition. Following the oral explanation and the debriefing and before the Committee's final opinion the sponsor chose to withdraw the application.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 16 January 2018, prior to final opinion.

2.1.2. Allogeneic CD4+ and CD25+ T lymphocytes *ex vivo* incubated with GP120-EMA/OD/150/17

Universitätsmedizin der Johannes Gutenberg-Universität Mainz; Treatment in haematopoietic stem cell transplantation

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:

- Intention to diagnose, prevent or treat

The sponsor is invited to clarify the envisaged clinical positioning of the proposed product: prevention of graft-versus-host disease (GvHD) as suggested by the provided nonclinical data or treatment of GvHD as suggested by the presented clinical development plan. Note that this is for the purposes of the delineation of the adequate orphan condition and indication; the sponsor's attention is drawn to the Orphan regulations and relevant guidelines (especially section A of ENTR/6283/00). In general, data would be expected to support the use in the envisaged orphan condition/indication.

To establish correctly if there exists a scientific rationale for the development of the proposed product, the sponsor should further discuss the absence of efficacy data with the proposed product- regulatory T cells that are activated by GP120.

- Significant benefit

The sponsor is requested to present a data-driven argumentation of significant benefit over authorised products for the orphan indication including Zalmoxis.

In the written response, and during an oral explanation before the Committee on 16 January 2018, the sponsor discussed the proposed cell therapy product and its clinical positioning in the prevention and treatment of graft-versus-host disease. The sponsor and the COMP agreed that the condition should be changed to “haematopoietic stem cell transplantation” with the orphan indication “treatment in haematopoietic stem cell transplantation”.

The sponsor presented additional non-clinical data from valid models showing that treatment with the proposed product was able to reduce graft-versus-host disease, which was accepted by the COMP as sufficient evidence for medical plausibility.

Regarding significant benefit, the sponsors outlined that the product would be able to treat graft-versus-host disease patients that are refractory to the current best standard of care including authorised products. This assumption was supported by bibliographical clinical data of similar products. Furthermore, the mechanism of action and clinical positioning of the product in the prevention setting would be different to currently used donor T lymphocyte products including the authorised product Zalmoxis. The COMP considered that this would be sufficient evidence for significant benefit for the purpose of orphan designation.

Following review of the application by the Committee, it was agreed to rename the indication to treatment in haematopoietic stem cell transplantation and to rename the active substance to allogeneic CD4+ and CD25+ T lymphocytes *ex vivo* incubated with GP120.

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 CD4+ and CD25+ T lymphocytes *ex vivo* incubated with GP120 was considered justified based on non-clinical data from relevant models demonstrating that treatment with the product was able to prevent and treat graft-versus-host disease.

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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic CD4+ and CD25+ T lymphocytes *ex vivo* incubated with GP120 will be of significant benefit to those affected by the condition. The sponsor has provided non-clinical data from relevant models demonstrating that treatment with the product was able to prevent and treat graft-versus-host disease. Bibliographical clinical data supported a clinical positioning that differs from currently authorised products for the

treatment in haematopoietic stem cell transplantation. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic CD4+ and CD25+ T lymphocytes *ex vivo* incubated with GP120, for treatment in haematopoietic stem cell transplantation, was adopted by consensus.

2.1.3. - EMA/OD/195/17

Prevention of radiotherapy-induced oral mucositis in head and neck cancer patients

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 1 January 2018, prior to responding to the list of issues.

2.1.4. 6-{[(1R,2S)-2-aminocyclohexyl]amino}-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-one monocitrate - EMA/OD/193/17

Takeda Pharma A/S; Treatment of acute myeloid leukaemia

COMP coordinator: Frauke Naumann-Winter

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 appears to have provided an underestimate of the current point prevalence of the condition. The sources of data used appear to be outdated and survival appears to have improved at 5yrs which has not been considered.

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.

- 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 is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. Particular consideration should be given regarding midostaurin.

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, the sponsor revised the prevalence calculation to 1.4 in 10.000 which is more in line with recent decisions and acceptable.

The sponsor also provided more information on baseline characteristics, prior treatment and results of the clinical trial. The proposed product achieved significant FLT3 target inhibition in patients with relapsing/refractory disease, and resulted in clinical responses, as measured by peripheral and bone marrow blast count reduction and by objective response in both FLT3 mutated and wild type disease. In addition, the sponsor compared the clinical single agent experience of midostaurin (authorised only in combination with standard induction treatment in newly diagnosed patients) to the single agent experience with the proposed product (cross-trial, historical/external control). With midostaurin, no CR or CRi had been observed in a relapsing/refractory FLT3-mutated population. The COMP concluded that significant benefit over midostaurin is plausible in view of activity in FLT3-WT patients with relapsing/refractory disease and who had been pre-treated with many different drugs. The COMP was of the opinion that it could recommend granting the orphan designation.

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

The intention to treat the condition with the medicinal product containing 6-{[(1R,2S)-2-aminocyclohexyl]amino}-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-one monocitrate was considered justified based on preliminary clinical data showing clinically relevant responses in patient outcomes.

The condition is life-threatening and chronically debilitating due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated intravascular coagulation and the risk of severe infections. The condition progresses rapidly and is fatal if left untreated.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 6-{[(1R,2S)-2-aminocyclohexyl]amino}-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-one monocitrate will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a clinically relevant effect in patients who have been previously heavily pretreated. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 6-{[(1R,2S)-2-aminocyclohexyl]amino}-7-fluoro-4-(1-methyl-1H-pyrazol-4-yl)-1,2-dihydro-3H-pyrrolo[3,4-c]pyridin-3-one monocitrate, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.1.5. - EMA/OD/171/17

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 19 December 2017, prior to responding to the list of issues.

2.1.6. - EMA/OD/305/16

Treatment of ovarian cancer

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

- Intention to treat

The sponsor in invited to elaborate on the comparability of the product subject of this application to the products referred in bibliography studies discussed for the purpose of establishing medical plausibility.

- Prevalence

The sponsor is invited to elaborate on:

a) the inclusion of fallopian and primary peritoneal cancer in the estimate,

b) the choice of the epidemiological index and the duration of the condition and

c) the available RARECARE data.

- 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 available other options for this population and d) how do those products compare in that population based on clinically relevant outcomes. Any updated data from non-clinical or clinical studies are invited to be added to the submission.

In the written response, and during an oral explanation before the Committee on 17 January 2018, the sponsor provided a table juxtaposing preparation protocols from different publications in order to address the comparability issue raised by the COMP.

It was stated that all protocols use minced tumour and sometimes ascites or pleural effusion to isolate tumour infiltrating lymphocytes but the initial cultures slightly differ between studies. Differences in IL-2 doses and treatment with anti-CD3 were acknowledged by the sponsor between the studies, but it was assumed that the differences in the protocols may influence the expansion of T cells that do not react to the tumour (non-tumour specific) and the later expansion phase. The COMP considered that the differences between the products would not allow for extrapolations, and therefore only the study with the specific product would have to be considered for the purpose of medical plausibility.

For the issue of prevalence, the applicant did not include fallopian and primary peritoneal cases in the calculations. The sponsor also did not specify the duration of the condition and only provided partial prevalence figures for adenocarcinoma from RARECARE (instead of full point prevalence for all types of ovarian cancer including primary peritoneal and fallopian). The COMP considered that the prevalence criterion has not been therefore justified.

For the issue of significant benefit, the sponsor envisions a second (and above) line, but no data are available or presented in any detail.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 January 2018, prior to final opinion.

2.1.7. – EMA/OD/170/17

Treatment of soft tissue sarcoma

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

Please provide a complete prevalence calculation including GIST and Kaposi sarcoma.

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".

- Significant benefit

Significant benefit is not substantiated with any data. The sponsor is requested to substantiate with data the arguments provided for significant benefit- of particular interest are benefits versus current adjuvant therapy approaches.

In the written response, and during an oral explanation before the Committee on 17 January 2018, the sponsor did not present additional data in support of significant benefit. The sponsor however argued that the proposed product will be added to the current best standard of care. Therefore, the added benefit would be implied by the already presented non-clinical safety and efficacy studies, which do not allow for a comparative discussion versus best standard of care including authorised products. The COMP was of the opinion that insufficient evidence was presented at this stage for the demonstration of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 17 January 2018, prior to final opinion.

2.1.8. Human monoclonal IgG2 antibody against tissue factor pathway inhibitor - EMA/OD/189/17

Bayer AG; Treatment of haemophilia A

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:

- Significant benefit

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

The issue of relative impact of the product compared to the authorised counterparts on quality of life in affected patients, the potential for improved efficacy based on the new mechanism of action, and the pathogen safety issues are expected to be discussed in the context of data from non-clinical or clinical studies.

In the written responses, the sponsor provided additional arguments for the demonstration of significant benefit. More data were provided supporting a clinically relevant advantage. The sponsor confirmed that patients with factor VIII inhibitors have been included in the clinical study, and that data are available following a single dose of the proposed product from 24 non-inhibitor subjects and 2 inhibitor subjects with high titre inhibitors. Versus the bypassing agents, the applicant observes an improved pro-thrombotic risk, by directly

comparing the products in non-clinical models. The COMP considered this to be a clinically relevant advantage in particular for patients with inhibitors.

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

The intention to treat the condition with the medicinal product containing human monoclonal IgG2 antibody against tissue factor pathway inhibitor was considered justified based on non-clinical observations supporting improved survival in models of the condition, and preliminary clinical observations supporting improved thrombin generation in affected patients.

The condition is chronically debilitating due to recurrent bleedings in joints, gastrointestinal tract or in surgery, which may be also be life-threatening.

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 human monoclonal IgG2 antibody against tissue factor pathway inhibitor will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data supporting a sustained reduction of tissue factor pathway inhibitor levels in affected patients, including observations in patients with Haemophilia A who had developed inhibitors to factor VIII. In addition, the sponsor has provided non-clinical data in an *in vivo* model of the condition, supporting reduced stasis-triggered thrombus generation compared to bypassing agents. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for human monoclonal IgG2 antibody against tissue factor pathway inhibitor, for treatment of haemophilia A, was adopted by consensus.

2.1.9. - EMA/OD/190/17

Treatment of haemophilia B

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 2 January 2018, prior to responding to the list of issues.

2.1.10. - EMA/OD/173/17

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

In order to justify the medical plausibility of the proposed product the applicant is invited to further elaborate on:

  – the relevance of the results obtained in an acute model of *Pseudomonas aeruginosa* infection to the intended clinical use of the product, which is assumed to be chronic infection/colonisation;

- the clinical relevance of *klebsiella pneumoniae* infection in cystic fibrosis;
- the relation between the efficacious dose used in the non-clinical studies and the expected doses of the product in the intended clinical use.

- Significant benefit

In order to justify the significant benefit of the proposed product the sponsor is invited to further discuss the results of the non-clinical studies and in particular the relative efficacy of the proposed product vis a vis tobramycin in the *pseudomonas aeruginosa* infection model and vis a vis colistin in the *Klebsiella pneumoniae* infection model.

The sponsor is also invited to further elaborate on any available data suggesting a potential clinical benefit of the proposed product in relation to the current standard of care for the treatment of infections in cystic fibrosis, including potential advantages in multidrug resistant infections.

In the written response, and during an oral explanation before the Committee on 17 January 2018, the sponsor further discussed the non-clinical model used for establishing medical plausibility, and the results of the study. The sponsor argued that no models of chronic infection with *Pseudomonas aeruginosa* are feasible. However the COMP objected that such models exist and have been presented in previous applications. In relation to significant benefit no additional grounds could be identified in the non-clinical studies that would show an advantage of the proposed product in relation to the currently authorised treatments for cystic fibrosis, with particular focus on *pseudomonas aeuruginosa* infection. The sponsor discussed non-clinical *in vitro* data showing efficacy of the proposed product in some strains of multidrug resistant bacteria that are relevant in cystic fibrosis. However the results were not consistent and the potential of *in vitro* data of minimum inhibitory concentration for translation into clinical efficacy is debatable.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 January 2018, prior to final opinion.

2.1.11. - EMA/OD/178/17

Treatment of Stargardt's disease

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 21 December 2017, prior to responding to the list of issues.

2.1.12. - EMA/OD/180/17

Treatment of acromegaly

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 4 January 2018, prior to responding to the list of issues.

2.1.13. Flucytosine - EMA/OD/198/17

Richardson Associates Regulatory Affairs Ltd; Treatment of glioma

COMP coordinator: Katerina Kopečková

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

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the clinical results to justify the assumption of significant benefit over carmustine wafers (Gliadel).

In the written response, the sponsor provided additional data to support significant benefit over carmustine wafers. A published meta-analysis of 30 studies of carmustine wafer therapy in the recurrent setting indicates that there is a survival benefit of 9.7 months. The provided preliminary clinical data of the combination therapy of vocimagene amiretrorepvec and flucytosine compares favourably with a median survival of 14.4 months in the recurrent setting. The COMP concluded that the provided indirect evidence is sufficient to support the assumption of significant benefit over carmustine wafers and cancelled the oral explanation. The sponsor is recommended to seek protocol assistance on the clinical development and the demonstration of significant benefit with a question to the COMP.

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

The intention to treat the condition with the medicinal product containing flucytosine was considered justified based on preliminary clinical data showing that patients responded to treatment with the proposed product when administered in combination with a product containing vocimagene amiretrorepvec.

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

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing flucytosine will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that recurrent glioma patients responded to treatment with the proposed product when administered in combination with a product containing vocimagene amiretrorepvec. The patients were recurrent to best standard of care including authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for flucytosine, for treatment of glioma, was adopted by consensus.

2.1.14. Vocimagene amiretrorepvec - EMA/OD/185/17

Richardson Associates Regulatory Affairs Ltd; Treatment of glioma

COMP coordinator: Katerina Kopečková

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

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the clinical results to justify the assumption of significant benefit over carmustine wafers (Gliadel).

In the written response, the sponsor provided additional data to support significant benefit over carmustine wafers. A published meta-analysis of 30 studies of carmustine wafer therapy in the recurrent setting indicate that the there is a survival benefit of 9.7 months. The provided preliminary clinical data of the combination therapy of vocimagene amiretrorepvec and flucytosine compares favourably with a median survival of 14.4 months in the recurrent setting. The COMP concluded that the provided indirect evidence is sufficient to demonstrate significant benefit over carmustine wafers and cancelled the oral explanation. The sponsor is recommended to seek protocol assistance on the clinical development and the demonstration of significant benefit with a question to the COMP.

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

The intention to treat the condition with the medicinal product containing vocimagene amiretrorepvec was considered justified based on preliminary clinical data showing that patients responded to treatment with the proposed product when administered in combination with a product containing flucytosine.

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

The condition was estimated to be affecting approximately 2.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing vocimagene amiretrorepvec will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that recurrent glioma patients responded to treatment with the proposed product when administered in combination with a product containing flucytosine. The patients were recurrent to best standard of care including authorised treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for vocimagene amiretrorepvec, for treatment of glioma, was adopted by consensus.

2.1.15. - EMA/OD/191/17

Treatment in cardiopulmonary by-pass

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 COMP is of the opinion that a technique used in cardiac surgery, such as cardiopulmonary bypass, should be justified as orphan condition/treatment modality in the context of the orphan designation.

The sponsor intends to use the product to prevent potential clinical consequences of cardiopulmonary bypass, in particular respiratory consequences. It is not clearly understood what 'treatment' in the proposed condition would refer to. The sponsor is therefore invited to further clarify how the intended clinical use of the product would fit within an orphan designation under a treatment indication.

In addition, as discussed during the previous submission, different pathogenetic mechanisms may be co-determinants of damage to the lungs and other organs during surgery involving cardiopulmonary bypass. Some factors identified in the literature include general anaesthesia, median sternotomy incision, internal mammary artery dissection, and the use of topical cooling for myocardial protection. Duration and type of mechanical ventilation may also play a role.

The sponsor is therefore invited to justify why cardiopulmonary bypass should be considered a distinct entity/treatment modality, i.e. separate from all the other factors that may influence the development of post-surgery complications (in particular lung dysfunction, as targeted by the sponsor).

- Intention to diagnose, prevent or treat

The authors of the publication of the randomized controlled trial in 40 pediatric patients presented by the sponsor identified factors in the study that may have had an impact on the post-operative development of pulmonary hypertension, such as the significantly longer cardiopulmonary bypass runs, significantly longer crossclamp times, and significantly more postoperative blood loss in the pulmonary hypertension group.

The sponsor is invited to discuss how these factors may impact on the conclusions that the differences in post-operative pulmonary hypertension are due to the proposed treatment.

The sponsor is also invited to discuss potential risk factors for the development of post-operative lung complications in the context of the clinical study performed by the applicant.

- Number of people affected

The condition remains to be justified as a valid condition for designation, and the incidence calculations are in relation to the condition as currently proposed by the sponsor.

The sponsor is invited to present more recent data based on their justification of the condition. While EU-wide recent statistics may not exist, data may be available from national registries or publications that could help calculating a more up-to date estimate.

In addition, as previously recommended, given the uncertainty about many of the assumptions regarding the incidence, and the fact that the proposed value is above 4 in 10,000, the sponsor should perform a sensitivity analysis of the reported calculations.

In the written response, and during an oral explanation before the Committee on 18 January 2018, the sponsor further discussed the issues raised by the COMP.

In relation to the condition, the sponsor re-stated the potential clinical consequences of cardiopulmonary bypass that the sponsor intends to prevent with the proposed product, mainly pulmonary hypertension and acute respiratory distress/lung dysfunction. These

clinical consequences are considered by the COMP as the target of the orphan designation, while cardiopulmonary bypass is not admissible as an orphan condition. In relation to medical plausibility the COMP was of the opinion that the sponsor did not present sufficient data to demonstrate that the effects of the product shown in the clinical studies so far are attributable only to the proposed product, since no data on potential variable known to influence the outcome of cardiac bypass surgery have been presented.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 January 2018, prior to final opinion.

2.1.16. - EMA/OD/176/17

Treatment of Myasthenia Gravis

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 disease modifying effect in the condition. The data currently provided is considered insufficient to support the assumption of significant benefit at the time of orphan designation.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from non-clinical 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 18 January 2018, the sponsor provided further results from the experiments on the EAMG non-clinical model. The results lent further support to the medical plausibility. With regard to the significant benefit, the sponsor provided a more detailed and structured discussion. Significant benefit against acetylcholine esterase inhibitors is argued on the basis of a potentially disease modifying and long term effect of the product. Significant benefit against immunosuppressants (prednisone and azathioprine) is argued on safety grounds. Significant benefit against plasmapheresis and IvIg is argued on safety grounds and on the basis of the potentially disease modifying and long term effect of the product. Significant benefit against eculizumab is argued on the basis that eculizumab is only indicated in a subpopulation of MG patients and also on safety grounds. The sponsor has provided a theoretical discussion to support significant benefit. The arguments, however, are based on the presumed disease modifying effect of the product based on its novel mechanism of action. No data driven comparative discussion has been provided.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 18 January 2018, prior to final opinion.

2.1.17. Mertansine functionalised gold nanoconjugate - EMA/OD/312/16

Midatech Pharma Plc; Treatment of hepatocellular carcinoma

COMP coordinator: Daniel O'Connor

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's calculation is not very clear and the sponsor has not provided a specific figure.

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

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

In the written response, the sponsor proposed a prevalence estimate between 0.6- 1.5 in 10,000. The COMP accepted the higher estimate of 1.5 in 10,000.

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

The intention to treat the condition with the medicinal product containing mertansine functionalised gold nanoconjugate was considered justified based on non-clinical data in a model of the condition showing reduction in tumor size.

The condition is life-threatening and chronically debilitating due to increased mortality and liver dysfunction. Median survival without therapy can be greater than 36 months for stage 0 and A, 16 months for stage B, 4-8 months for stage C and less than 4 months for stage D.

The condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing mertansine functionalised gold nanoconjugate will be of significant benefit to those affected by the condition. The sponsor has provided nonclinical *in vivo* data comparing the product to the authorised product, which demonstrate that the product inhibits tumour growth to a higher degree. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for mertansine functionalised gold nanoconjugate, for treatment of hepatocellular carcinoma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. - EMA/OD/208/17

Treatment of C3 glomerulopathy

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 February meeting.

2.2.2. (R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonate dehydrate - EMA/OD/203/17

Chiesi Farmaceutici S.p.A.; Treatment of cystic fibrosis

COMP coordinator: Kerstin Westermark

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 (R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonate dehydrate was considered justified based on data showing reduction of airways inflammatory cells and of bacterial burden of *Pseudomonas aeruginosa* with the proposed product in preclinical models of the condition.

The condition is chronically debilitating and life threatening due to 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidin-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonate dehydrate will be of significant benefit to those affected by the condition. This is based on data from *in vivo* models of the condition showing reduction of the airways inflammatory burden resulting in increased antibiotic activity of tobramycin, currently authorised for the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for (R)-2-(5-cyano-2-(6-(methoxycarbonyl)-7-methyl-3-oxo-8-(3-(trifluoromethyl)phenyl)-2,3,5,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrimidine-5-yl)phenyl)-N,N,N-trimethylethanaminium methanesulfonate dehydrate, for treatment of cystic fibrosis, was adopted by consensus.

2.2.3. 1-[[[4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yl]oxy]methyl]cyclopropanamine- dihydrochloride - EMA/OD/202/17

CATS Consultants GmbH; Treatment of soft tissue sarcoma

COMP coordinator: 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 1-[[[4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yl]oxy]methyl]cyclopropanamine-dihydrochloride was considered justified based on preliminary clinical data showing responses in patients affected by the condition.

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 3.7 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 1-[[[4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yl]oxy]methyl]cyclopropanamine-dihydrochloride will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing responses in patients affected by the condition. Indirect comparisons were provided to demonstrate that the preliminary outcomes compare favourably with authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1-[[[4-(4-fluoro-2-methyl-1H-indol-5-yloxy)-6-methoxyquinolin-7-yl]oxy]methyl]cyclopropanamine-dihydrochloride, for treatment of soft tissue sarcoma, was adopted by consensus.

2.2.4. 2'-O-(2-methoxyethyl) modified antisense oligonucleotide targeting exon 13 in the USH2A gene - EMA/OD/197/17

ProQR Therapeutics IV BV; Treatment of retinitis pigmentosa

COMP coordinator: Violeta Stoyanova

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 2'-O-(2-methoxyethyl)-modified antisense oligonucleotide targeting exon 13 in the USH2A gene was considered justified based on non-clinical data in a valid model of the disease suggesting improved retinal function.

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

The condition was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for 2'-O-(2-methoxyethyl)-modified antisense oligonucleotide targeting exon 13 in the *USH2A* gene, for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.5. Adenovirus associated viral vector serotype 8 containing the human RPGR gene - EMA/OD/220/17

Nightstar Therapeutics plc; Treatment of retinitis pigmentosa

COMP coordinator: Armando Magrelli

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 adenovirus-associated viral vector serotype 8 containing the human RPGR gene was considered justified based on non-clinical *in vivo* data in a valid model of the disease demonstrating improved retinal function.

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

The condition was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for adenovirus-associated viral vector serotype 8 containing the human *RPGR* gene, for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.6. - EMA/OD/204/17

Treatment of graft-versus-host disease

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

2.2.7. Cannabidivarin - EMA/OD/215/17

GW Research Ltd; Treatment of Fragile X Syndrome

COMP coordinator: Dinah Duarte

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

The intention to treat the condition with the medicinal product containing cannabidivarin was considered justified based on the results of studies in a valid non-clinical *in vivo* model of the disease which shows an improvement in behavioural outcomes.

The condition is chronically debilitating due to developmental delay, severe neurobehavioral and neurocognitive complications.

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

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

A positive opinion for cannabidivarin, for treatment of fragile X syndrome, was adopted by consensus.

2.2.8. - EMA/OD/062/17

Treatment of Dravet 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 February meeting.

2.2.9. - EMA/OD/219/17

Treatment of Friedreich's ataxia

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 February meeting.

2.2.10. - EMA/OD/172/17

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 respond in writing before the Committee February meeting.

2.2.11. - EMA/OD/210/17

Treatment of NTRK-fusion non-small-cell lung cancer

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

2.2.12. - EMA/OD/212/17

Treatment of papillary thyroid 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 February meeting.

2.2.13. - EMA/OD/209/17

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 February meeting.

2.2.14. - EMA/OD/213/17

Treatment of salivary gland 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 February meeting.

2.2.15. - EMA/OD/211/17

Treatment of pancreatic cancer

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

2.2.16. Levosimendan - EMA/OD/174/17

Orion Corporation; 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 levosimendan was considered justified based on preliminary clinical data supporting improved respiratory function in amyotrophic lateral sclerosis patients.

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

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing levosimendan will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in amyotrophic lateral sclerosis patients supporting an improvement in respiratory function, a manifestation which is not targeted by the authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for levosimendan, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.17. N-(tert-butylcarbamoyl)-5-cyano-2-((4'-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)oxy)benzenesulfonamide - EMA/OD/199/17

ATXA Therapeutics Limited; Treatment of pulmonary arterial hypertension

COMP coordinator: Eva Malikova

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

The intention to treat the condition with the medicinal product containing N-(tert-butylcarbamoyl)-5-cyano-2-((4'-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)oxy)benzenesulfonamide was considered justified based on preclinical *in vivo* data showing improvement of haemodynamic parameters and histology in valid models of the condition.

The condition is life-threatening and chronically debilitating due to progressive dyspnoea and right heart failure, leading to death in approximately 3 years after diagnosis.

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

In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing N-(tert-butylcarbamoyl)-5-cyano-2-((4'-(difluoromethoxy)-

[1,1'-biphenyl]-3-yl)oxy)benzenesulfonamide will be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing that the combination of the proposed product with sildenafil, currently authorised for the condition, results in better efficacy than sildenafil as monotherapy. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for N-(tert-butylcarbamoyl)-5-cyano-2-((4'-(difluoromethoxy)-[1,1'-biphenyl]-3-yl)oxy)benzenesulfonamide, for treatment of pulmonary arterial hypertension, was adopted by consensus.

2.2.18. - EMA/OD/181/17

Treatment of non-traumatic subarachnoid haemorrhage

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 February meeting.

2.2.19. - EMA/OD/206/17

Treatment of naevoid basal cell carcinoma syndrome (Gorlin 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 February meeting.

2.2.20. Pyridoxal 5'-Phosphate - EMA/OD/201/17

Medicure Pharma Europe Limited; Treatment of pyridoxamine 5'-phosphate oxidase deficiency

COMP coordinator: Vallo Tillmann

The Committee agreed that the condition, pyridoxamine 5'-phosphate oxidase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing pyridoxal 5'-phosphate was considered justified based on bibliographical data in patients with the condition.

The condition is life-threatening due to intractable seizures which may be fatal.

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

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

A positive opinion for pyridoxal 5'-phosphate, for treatment of pyridoxamine 5'-phosphate oxidase deficiency, was adopted by consensus.

2.2.21. Recombinant human monoclonal antibody against mannan-binding lectin-associated serine protease-2 - EMA/OD/200/17

Omeros London Limited; Treatment of primary IgA nephropathy

COMP coordinator: Dinko Vitezic

Following review of the application by the Committee, it was agreed to rename the indication to treatment of primary IgA nephropathy.

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

The intention to treat the condition with the medicinal product containing recombinant human monoclonal antibody against mannan-binding lectin-associated serine protease-2 was considered justified based on preliminary clinical observations in affected patients, who responded to treatment with improvement in proteinuria.

The condition is life-threatening and chronically debilitating due to progressive loss of kidney function leading to kidney failure requiring dialysis and transplantation.

The condition was estimated to be affecting approximately 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 recombinant human monoclonal antibody against mannan-binding lectin-associated serine protease-2, for treatment of primary IgA nephropathy, was adopted by consensus.

2.2.22. Rusalatide acetate - EMA/OD/221/17

Raremoon Consulting Ltd; Treatment of acute radiation syndrome

COMP coordinator: Geraldine O'Dea

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

The intention to treat the condition with the medicinal product containing rusalatide acetate was considered justified based on non-clinical data suggesting that the product is able to improve survival in relevant models of the condition.

The condition is life-threatening due to hematopoietic, gastrointestinal, neurological and vascular symptoms associated with multiple organ dysfunction leading to multiple organ failure and carcinogenesis.

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.

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 rusalatide acetate, for treatment of acute radiation syndrome, was adopted by consensus.

2.2.23. Seletalisib - EMA/OD/205/17

UCB Biopharma SPRL; Treatment of activated phosphoinositide 3-kinase delta syndrome

COMP coordinator: Dinah Duarte

The Committee agreed that the condition, activated phosphoinositide 3-kinase delta syndrome, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing seletalisib was considered justified based on preliminary clinical data showing a reduction in lymphoproliferation and improvement in lung function.

The condition is chronically debilitating due to recurrent respiratory infections, leading to bronchiectasis, progressive lymphopenia, and defective antibody production. In the more severe forms this leads to death.

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

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

A positive opinion for seletalisib, for treatment of activated phosphoinositide 3-kinase delta syndrome, was adopted by consensus.

2.2.24. - EMA/OD/222/17

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 February meeting.

2.2.25. - EMA/OD/217/17

Treatment of diffuse large B-cell 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 February meeting.

2.2.26. - EMA/OD/216/17

Treatment of soft tissue sarcoma

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 February meeting.

2.3. Revision of the COMP opinions

None

2.4. Amendment of existing orphan designations

None

2.5. Appeal

2.5.1. Melatonin – EMA/OD/039/17

Therapicon Srl; Treatment of partial deep dermal and full thickness burns

COMP appeal coordinator: Armando Magrelli

In the grounds for appeal, and during an oral explanation before the Committee on 16 January 2018, the sponsor indicated the multidisciplinary nature of the management of deep dermal and full thickness burns. They noted that it is acknowledged that there are national variations regarding how patients with these types of burns are managed and that the appropriate management of the burn patients remains a major challenge. The COMP noted that the treatment of partial to full depth burns is a complex management issue and covering many different aspects such as pain management, wound management, systemic management and psychological management. There are several products which are authorised in the EU for use in the treatment of burns which are primarily focused on wound management. These are povidone iodine, sodium hypochlorite, silver sulfadiazine (Flammazine) and Nexobride. The Sponsor highlighted the use of Flammazine in Europe as part of the standard of care during the appeal procedure.

The sponsor resubmitted the same bibliographical reference as used during the initial procedure. This study was conducted by an investigator in an Iraqi hospital and involved 120 patients divided into 6 different treatment groups. The sponsor highlighted the standard of care used in the Iraqi hospital also defined as: “standard hospital policy” as the drug treatment given to all the treated groups patients in the burn unit included intravenous fluid such as Ringer’s solution and glucose water given according to the Parkland method. Patients also received, if required, systemic antibiotics and local antibiotic ointments were also given, according to availability in the hospital, including Flamazine, Tetracyclin, and Fucidin ointment. Other drugs given were analgesics, antipyretics, and others like diazepam and Tagamet.

The COMP discussed the similarities and differences with the EU standard of care which uses the authorised products povidone iodine, sodium hypochlorite, silver sulfadiazine and Nexobrid. It was noted that the use of povidone iodine, sodium hypochlorite and Nexobride were not included in the standard of care of the study presented by the sponsor. As these products were not included, the COMP noted that the clinically relevant advantage of using melatonin was difficult to establish within the European context.

The COMP therefore considers that the sponsor has failed to demonstrate that the product may be of significant benefit versus authorised methods of treatment in the EU.

A negative opinion for melatonin, for treatment of partial deep dermal and full thickness burns, was adopted by consensus.

2.6. Nominations

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

COMP coordinators were appointed for 17 upcoming applications.

2.7. Evaluation on-going

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

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of acute myeloid leukaemia

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 Niemann-Pick disease, type C

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

3.1.3. -

Treatment of mucopolysaccharidosis type I

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

3.1.4. -

TKI inhibitor for treatment of gastrointestinal stromal tumors

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 cutaneous T-cell lymphoma

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 diffuse large B-cell lymphoma

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

3.1.7. -

Treatment of multiple myeloma

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

3.1.8. –

Treatment of glioma

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

3.1.9. -

Treatment of multiple myeloma

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

3.1.10. -

Treatment of paroxysmal nocturnal haemoglobinuria

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

3.2. Finalised letters

3.2.1. -

Treatment of spinal muscular atrophy

The finalised letter was circulated for information.

3.2.2. -

Treatment of plasma cell myeloma

The finalised letter was circulated for information.

3.2.3. -

Treatment of sickle cell disease

The finalised letter was circulated for information.

3.2.4. -

Treatment of ornithine transcarbamylase deficiency

The finalised letter was circulated for information.

3.2.5. -

Treatment of Lennox-Gastaut syndrome

The finalised letter was circulated for information.

3.2.6. -

Treatment of mantle cell lymphoma

The finalised letter was circulated for information.

3.2.7. -

Treatment of myelodysplastic syndromes

The finalised letter was circulated for information.

3.2.8. -

Treatment of Leber's hereditary optic neuropathy

The finalised letter was circulated for information.

3.3. New requests

3.3.1. -

Treatment of adenosine deaminase-deficient-severe combined immunodeficiency

The new request was noted.

3.3.2. –

Treatment of acute hepatic porphyria

The new request was noted.

3.3.3. -

Treatment of adrenoleukodystrophy

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

Clovis Oncology UK Ltd; Treatment of ovarian cancer

The status of the procedure at CHMP was noted.

4.2.2. - metreleptin – EMEA/H/C/004218

Aegerion Pharmaceuticals Limited;

a) Treatment of familial partial lipodystrophy EMA/OD/033/12, EU/3/12/1022

b) Treatment of Barraquer-Simons syndrome EMA/OD/034/12, EU/3/12/1023

c) Treatment of Lawrence syndrome EMA/OD/035/12, EU/3/12/1024

d) Treatment of Berardinelli-Seip syndrome EMA/OD/036/12, EU/3/12/1025

The status of the procedure at CHMP was noted.

4.3. Appeal

4.3.1. Alofisel – darvadstrocel – EMEA/H/C/004258, EMEA/OD/054/09, EU/3/09/667

TIGENIX, S.A.U.; Treatment of anal fistula

COMP coordinator: Eva Malikova / Ingrid Wang

In its grounds for appeal, and during an oral explanation before the Committee on 16 January 2018, the sponsor further elaborated on the points raised in the previous discussions, mainly on the size of the patient population refractory to treatment with anti-TNFα and on the efficacy of Alofisel in this patient population. Points raised on the prevalence of the condition were also addressed. The COMP was positive on the grounds of the appeal. Five members signed a divergent opinion. A more detailed discussion will be available in the orphan maintenance assessment report published on the EMA website.

The COMP concluded that:

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

The prevalence of anal fistula (hereinafter referred to as “the condition”) is estimated to remain below 5 in 10,000 and was concluded to be less than 3.47 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating due to pain and itching, recurring local infection and abscess formation, perianal swelling, stool or blood from cutaneous fistula openings leading to social, sexual and employment restrictions and severely compromised quality of life.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Alofisel will be of potential significant benefit to those affected by the orphan condition is confirmed. This is based on clinical data from the phase 3 randomized placebo-controlled clinical trial showing significant clinical efficacy in patients

that were refractory to treatment with anti-TNFα medicinal products, currently authorised for the condition.

An opinion recommending not to remove Alofisel, darvadstrocel (EU/3/09/667) from the EC Register of Orphan Medicinal Products was adopted by majority (23 out of 28 votes).

The Icelandic and the Norwegian COMP members agree with the above-mentioned recommendation of the COMP. The divergent positions (*Katerina Kopečkova; Armando Magrelli; Daniel O'Connor; Violeta Stoyanova-Beninska; Kerstin Westermark)* were appended to this opinion.

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

4.3.2. Verkazia - ciclosporin – EMEA/H/C/004411, EMEA/OD/106/05, EU/3/06/360

Santen Oy; Treatment of vernal keratoconjunctivitis

Following a request for clarification with respect to the COMP opinion of 27 November 2017 by the European Commission on the 4 December 2017, the COMP adopted a revised final opinion. The criteria for designation as set out in Article 3(1)(b) were still not satisfied.

The COMP recommended, by consensus, that Verkazia, ciclosporin (EU/3/06/360) for treatment of vernal keratoconjunctivitis is removed from the Community Register of Orphan Medicinal Products.

4.4. On-going procedures

COMP co-ordinators were appointed for one application.

4.5. Public Summary of Opinions

Action: For information

4.6. Orphan Maintenance Reports

Action: For information

Document(s) tabled:
Prevymis Orphan Maintenance Assessment Report
Jorveza Orphan Maintenance Assessment Report
Adcetris (variation) Orphan Maintenance Assessment Report

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

5.1. After adoption of CHMP opinion

None

5.2. Prior to adoption of CHMP opinion

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

AstraZeneca AB - Sweden; Treatment of ovarian cancer

CHMP rapporteur: Alexandre Moreau

The status of the procedure at CHMP was noted.

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

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

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

The COMP agreed that a formal review of the maintenance of the orphan designation for the applied indication is needed.

5.3. Appeal

None

5.4. On-going procedures

None

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

None

7. Organisational, regulatory and methodological matters

7.1. Mandate and organisation of the COMP

7.1.1. COMP Strategic Review & Learning meeting, 26-28 March 2018, 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 16 January 2018.

7.1.3. Non-Clinical Working Group

The working group on Non-clinical Models met on 17 January 2018.

7.1.4. Condition Working Group

The working group on Condition met on 18 January 2018.

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 December 2017

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

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

Document was circulated in MMD.

Document tabled:
Meeting Summary PCWP meeting with all eligible organisations – 22 Nov

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

None

7.4. Cooperation within the EU regulatory network

7.4.1. European Commission

None

7.5. Cooperation with International Regulators

7.5.1. Food and Drug Administration (FDA)

None

7.5.2. Japanese Pharmaceuticals and Medical Devices Agency (PMDA)

None

7.5.3. 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

8.1. Preparedness of the system and capacity increase

8.2. S-REPS: a new way of supporting COMP procedures with a CRM (Customer Relationship Management software)

Action: For information

8.3. EMA Business Pipeline activity and Horizon scanning

Document was circulated in MMD.

Document tabled:
Upcoming Q4/2017 Update of the Business Pipeline report for the human scientific committees

8.4. PRIME products

The Committee was updated on the PRIME product list.

8.5. Concepts of significant benefit and relative effectiveness, EMA-EUnetHTA work plan Jan 2017 – May 2020

The Committee was updated on the concepts of significant benefit and relative effectiveness, EMA-EUnetHTA work plan Jan 2017 – May 2020.

9. Explanatory notes

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

Abbreviations / Acronyms

CHMP: Committee for Medicinal Product for Human Use

COMP: Committee for Orphan Medicinal Products

EC: European Commission

OD: Orphan Designation

PA: Protocol Assistance

PDCO: Paediatric Committee

PRAC: Pharmacovigilance and Risk Assessment Committee

SA: Scientific Advice

SAWP: Scientific Advice Working Party

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

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

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

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

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

Sponsor

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

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

At the time of marketing authorisation, the COMP will check if all criteria for orphan designation are still met. The designated orphan medicinal product should be removed from

the Community Register of Orphan Medicinal Products if it is established that the criteria laid down in the legislation are no longer met.

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

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 16-18 January 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	
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	
Geraldine O'Dea	Member	Ireland	No interests declared	
Armando Magrelli	Member	Italy	No interests declared	
Irena Rogovska	Member	Latvia	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
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	
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	Outcome restriction following evaluation of e-DoI	5.2.1
Ingeborg Barisic	Member	Expert recommended by EMA	No restrictions applicable to this meeting	
Giuseppe Capovilla	Member	Expert recommended by EMA	No interests declared	
Virginie Hivert	Expert - in person*	Patients' Organisation Representative	No restrictions applicable to this meeting	
Julian Isla	Expert - in person*	Patient expert	No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				

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