19 December 2015
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Procedure Management and Committees Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes for the meeting on 6-8 October 2015

Chair: Bruno Sepodes – Vice-Chair: Lesley Greene

06 October 2015, 09:00-19:30, room 3F

07 October 2015, 08:30-19:45, room 3F

08 October 2015, 08:30-16:20, room 3F

Disclaimers

Some of the information contained in this agenda 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 agenda is a working document primarily designed for COMP members and the work the Committee undertakes.

Note on access to documents

Some documents mentioned in the agenda 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).

[1] Minor corrections under section 4.1.2

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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 and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced that no restriction in the involvement of meeting participants was identified 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

COMP agenda for 6-8 October 2015 was adopted with no amendments.

1.3. Adoption of the minutes

COMP minutes for 1-3 September 2015 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. Interferon alfa-n3 - EMA/OD/093/15

NV Hemipsherx BioPharma Europe; Treatment of Middle East respiratory syndrome

COMP coordinator: Josep Torrent-Farnell

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 reports a reduction of viral load in infected cells with the proposed product administered before or after infection. However it is difficult to put the effects of the proposed product in perspective with the natural course of the infection. The sponsor is therefore invited to further elaborate on how the changes induced by the product on the viral load of infected cells *in vitro* relate to the viral load of untreated cells over time.

In addition the sponsor is invited to further elaborate on:

- the relation between viral load and clinical manifestations of the disease.

- the efficacious doses *in vitro* in relation to the expected dose for clinical use, based on previous experience with interferon treatment in viral infections.

- the rationale, advantages and disadvantages of the selected *in vitro* model.

In the written response the sponsor clarified the relevance of the preclinical experiments, and discussed the relation of viral loads of the Middle East Respiratory Syndrome Coronavirus (MERSCoV) with clinical disease in humans.

The applicant presented clinical observations supporting that the highest viral levels are found in the lower respiratory tract and in only a few cases viral shedding can be detected in low levels in urine, stool samples, and oro-nasal swabs. The sponsor also discussed the *in vitro* model used to support the plausibility, justifying the origin of used cells in the context of species specificity.

The COMP noted the limitation of the preclinical data being only *in vitro*, and reflected on the absence of *in vivo* models. After discussing the sponsor's answers the COMP decided that an oral explanation was not necessary.

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

The intention to treat the condition with the medicinal product containing interferon alfa-n3 was considered justified based on preclinical data showing antiviral activity of the product in cells infected with MERSCoV.

The condition is life-threatening and chronically debilitating due to the development of cough, fever, shortness of breath, diarrhoea, nausea, vomiting that can lead to severe illness, with pneumonia, respiratory distress syndrome and death in 35% of cases.

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.

Thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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 interferon alfa-n3, for treatment of Middle East respiratory syndrome, was adopted by consensus.

2.1.2. - EMA/OD/117/15

Treatment of intestinal malabsorption in pre-term infants

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 underlying condition 'intestinal malabsorption' of the proposed orphan condition is not clear and subsetting is assumed on the basis of the developmental stage. It should be noted

that a developmental stage in human development per se might not be considered a distinct medical entity.

Treatment of intestinal malabsorption in pre-term infants should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

The sponsor is invited to clarify

– If the proposed condition is considered a distinct medical entity. If so please discuss how it differs from all other types of intestinal malabsorption regarding pathophysiology, histopathology and clinical features. This should be supported by consensus classification/nosology.

– If the proposed condition is considered a subset. If so, please discuss to widen the orphan condition and discuss intestinal malabsorption as distinct medical entity in contrast to a clinical manifestation of various conditions. Subsequently, discuss the validity of the subset with the focus on those pathophysiological characteristics associated with this subset that are closely linked to the pharmacological action of the medicinal product in such a way that the absence of these characteristics will render the product ineffective in the rest of the population suffering from the condition.

- Number of people affected

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

In the written response, and during an oral explanation before the Committee on 7 October 2015, the sponsor further elaborated on the issues raised. With regards to the proposed condition, the sponsor revised the current proposal to: "gastro-intestinal immaturity associated intestinal malabsorption in pre-term infants" and outlined the distinctiveness to the other types of intestinal malabsorption in terms of pathophysiology. The pathophysiology of other type of malabsorption was discussed to be more related to enzymatic deficiencies and genetic defects, in contrast to the proposed orphan condition which is caused by a disruption of adequate growth and maturity of the gut. The sponsor was of the opinion that a disruption of development of the gastrointestinal tract in utero, irrespective of its cause, is not a naturally occurring physiological process, but a pathological deviation from the normal structure and function.

The COMP considered that the proposed condition could not be considered to be a distinct medical entity for the purpose of orphan designation. It was noted that the immaturity of the gastro-intestinal system per se could not be seen as a pathological entity, and there was no pathological condition for which the pre-term associated immaturity could be defined as cause. Therefore the sponsor has not delineated a distinct medical entity that would be valid for the purpose of orphan designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 October 2015, prior to final opinion.

2.1.3. - EMA/OD/069/15

Treatment of glioma

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

- Number of people affected

The sponsor is invited to re-calculate the prevalence of the proposed orphan condition based on recent epidemiological studies and registers, and present the **total number of people** affected by the condition per 10 000 within the European Union. 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".

- Significant benefit

The assumption of significant benefit is argued on the potential of improved efficacy in a subset of the population (temozolomide resistant patients). However no *in vivo* data are presented to allow for drawing conclusions *vis a vis* temozolomide. Therefore the sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the *in vivo* 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 7 October 2015, the sponsor presented additional calculations regarding the prevalence of the proposed condition, but did not include any additional data (compared to the original application) to justify the criterion of significant benefit. The sponsor mentioned that they recently obtained survival data *in vivo* but since these were not provided or presented, they could not be further discussed. The COMP considered that in the absence of data to support a clinically relevant advantage in temozolomide resistant patients, the assumption of significant benefit had not been justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 October 2015, prior to final opinion.

2.1.4. - EMA/OD/081/15

Treatment of diffuse large B-cell lymphoma

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 diffuse large B-cell lymphoma, the sponsor should further elaborate on the preliminary observations of the clinical study presented herein and discuss the extent to which the results obtained may be attributed to valproic acid and not to other concomitant chemotherapy used in the study.

- Significant benefit

The sponsor is requested to further discuss the indirect comparison performed to support the notion of improved efficacy. A discussion of the populations and results compared is expected.

In the written response, and during an oral explanation before the Committee on 7 October 2015, the sponsor discussed the response criteria used in the preliminary clinical study, and provided a justification of the indirect comparison. It was stressed that the complete response rate for all patients was approximately 50% higher than the historical comparator presented. It was also pointed out that due to the evolution of response criteria over time to include functional imaging, complete responses in older studies may be over-represented compared to newer studies. It was however also stated that the groups were of the same age but the stages of the patients of the comparator study were higher.

The COMP considered that the response rates observed by the sponsor in their study may have been attributed solely to the R-CHOP administration to which the proposed product was added on. The indirect comparison was not clear given the differences in the populations studied and the extent of the effects observed, and in the absence of controls, the proof of concept of the product in the applied condition was yet to be presented.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 October 2015, prior to final opinion.

2.1.5. - EMA/OD/120/15

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:

- Intention to diagnose, prevent or treat

In the application, the sponsor has provided data on the changes that the product induces in acute myeloid leukaemia cell survival. Nevertheless the relationship between these measurements and the choice to develop the product only for paediatric population has not been adequately justified.

The sponsor should elaborate on all existing data, which would support the exclusion of adult population from the treatment of relapsed acute myeloid leukaemia with the proposed product.

- Number of people affected

The sponsor presented estimates from two large European cancer registry studies and proposes a number reflecting the annual incidence rate rather than the prevalence. The proposed number of persons affected by the condition in the EU is thus most likely an underestimate.

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 given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

- Significant benefit

The sponsor bases the argument for significant benefit largely on preclinical *in vivo* relapse studies. Sponsors conclusion about the comparative efficacy of echinomycin is based on an assumption that the relapsed acute myeloid leukaemia in mice is resistant to existing authorised treatments. This data does not allow the identification of patient groups who could benefit from the treatment with echinomycin. It is also not clear why only paediatric population would be included in the treatment indication.

The sponsor should further elaborate on why the results from their submitted data support the significant benefit assumption within the context of the current therapeutic management of patients, particularly regarding the proposal of only treating the paediatric population that is refractory to other existing authorised treatments.

In the absence of a discussion of relevant submitted data within the context of the use of all authorized products significant benefit cannot be ascertained. Therefore, the sponsor is invited to review and discuss the list of all products authorized in the European Union, which was incomplete in this application.

In the written response, and during an oral explanation before the Committee on 7 October 2015, the sponsor addressed the questions raised by the committee. The envisioned therapeutic indication of the product was in the population of paediatric refractory AML, but it was clarified that this does not preclude the development of the drug for the condition as a whole. With regards to the prevalence, the applicant provided an amended calculation of the prevalence and proposed the 5 year partial prevalence to be around 0.9 in 10,000 people in the EU. As for significant benefit, the sponsor recapitulated the argumentation presented in the original submission supporting the significant claim based on the novel mechanism of action as well as the use in a relapse/refractory population for whom treatment options are limited.

The committee reflected on the usefulness of the pre-clinical data presented to draw conclusions for the justification of significant benefit. It was pointed out that there was a lack of indirect or direct comparisons which would support improved efficacy versus other products. The sponsor claimed to have tested a battery of other products which were not efficacious in the same pre-clinical model, but no data to this end were presented for the assessment by the committee. Similarly, no information on the nature of pre-treatment of tested cells from patients was provided to support the claim of resistance to particular treatments. The committee considered that this level of evidence is not sufficient to support an assumption significant benefit and that a comparative discussion vis a vis authorised treatments would be necessary to justify the significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 7 October 2015, prior to final opinion.

2.1.6. Humanised fusion protein consisting of extracellular domain of CD24 linked to IgG1 Fc domain - EMA/OD/119/15

Enpharma Ltd; Prevention of graft-versus-host disease

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:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for prevention of graft-versus-host disease, the sponsor should further elaborate on the mechanism of action of the proposed product and provide any available evidence supporting its scientific rationale in the proposed condition.

In addition the sponsor is invited to further clarify the methodology and results of the preclinical studies and discuss the rationale and advantages of using a chimeric model for the preclinical proof of efficacy of the product.

- Significant benefit

In order to support the significant benefit the sponsor is invited to further discuss the proposed clinical use of the product in relation to what is currently already authorized for the condition, based on the mechanism of action and any available data so far.

In the written response, and during an oral explanation before the Committee on 7 October 2015, the sponsor expanded on the role of damage associated molecular patterns (DAMPs) in the pathophysiology of the proposed condition and clarified the preclinical experiments proposed as support to the medical plausibility, including a justification of the chimeric model used.

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

The intention to prevent the condition with the medicinal product containing humanised fusion protein consisting of extracellular domain of CD24 linked to IgG1 Fc domain was considered justified based on preclinical data showing improved survival.

The condition is chronically debilitating and life-threatening due to the potential development of severe intestinal inflammation with diarrhoea, abdominal pain, nausea and vomiting, skin rash and necrosis of the mucosa. Mortality can reach 100% in severe forms not responding to immunosuppressive treatment.

The population of patients eligible for prevention of the condition was estimated to be approximately 0.3 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing humanised fusion protein consisting of extracellular domain of CD24 linked to IgG1 Fc domain may be of significant benefit to the population at risk of developing the condition. The sponsor has provided preclinical data showing increased survival with the proposed product in models of the condition. The new mechanism of action of the product, offering the potential of being used in combination with the currently authorised treatments for the condition, could translate into a clinically relevant advantage for the patients at risk of graft versus host disease. The Committee concludes that this constitutes a clinically relevant advantage for the patients at risk of developing the condition.

A positive opinion for humanised fusion protein consisting of extracellular domain of CD24 linked to IgG1 Fc domain, for treatment of prevention of graft-versus-host disease, was adopted by consensus.

2.1.7. - EMA/OD/091/15

Treatment of adrenal insufficiency

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

- 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 adrenal insufficiency, the sponsor should further elaborate on the relevance of other products containing dyes or saline, to draw conclusions for the proposed product as applied for designation.

- 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 a) clarify if all causes of adrenal insufficiency are included in the calculation, including tertiary insufficiency b) provide a sensitivity analysis of all assumptions based on worst case scenarios and c) discuss any epidemiological changes since the time of the referred studies. Please consider the publication Charmandori et al, 2014 in this regard.

- Significant benefit

The arguments on significant benefit are based on the potential major contribution to patient care in patients affected by acute adrenal crisis.

The sponsor is requested to further discuss the arguments provided for significant benefit and in particular to i) quantify the outcomes of failed self-administration based on data of current standard of care, ii) provide data to support improvement of such outcomes and iii) provide any available data with the proposed product as applied for designation.

In the absence of such data, significant benefit cannot be established.

In the written response, and during an oral explanation before the Committee on 8 October 2015, the sponsor addressed the issues raised. It was confirmed that no further data exist, and that no product containing hydrocortisone has been tested so far. With regards to the prevalence calculation, it was asserted that tertiary cases can be considered of negligible importance for the calculation, and a sensitivity analysis was presented that spanned figures on the non-permissible side of the threshold for the worst case scenarios. With significant benefit, the sponsor stated that "Only the feeling of the patients and the professionals can be used to estimate the improvement of the patient compliance and the quality of life of the patients". A demonstration of the device to be used in the future was carried out before the committee during the oral explanation.

The COMP was of the opinion that notwithstanding the necessary requirement of filing an application at any stage of development, the condition of establishing the criteria for designation based on data was not met. It was stressed that no data were presented to address the issues raised and in particular that the prevalence criterion was not justified. The sensitivity analysis of the prevalence calculation challenges the provisioned threshold and should include all the population with adrenal insufficiency.

Therefore, the criteria for orphan designation could not be considered met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 October 2015, prior to final opinion.

2.1.8. 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)-[1,1'-biphenyl]-2-sulfonamide - EMA/OD/115/15

Retrophin Europe Limited; Treatment of focal segmental glomerulosclerosis

COMP coordinator: Josep Torrent-Farnell

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

- Number of people affected

The sponsor has submitted a calculation primarily based on the Primary Focal Segmental Glomerulosclerosis.

As it seems that the sponsor has excluded part of the population affected by condition namely the secondary forms of the condition, the sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

In the written response, the sponsor provided an updated written prevalence calculation which included secondary forms of the condition based on a literature search. The sponsor also offered a sensitivity analysis of the assumptions used.

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

The intention to treat the condition with the medicinal product containing 4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)-[1,1'-biphenyl]-2-sulfonamide was considered justified based on a pre-clinical *in vivo* model of the condition showing an improvement in renal function.

The condition is life-threatening and chronically debilitating due to the development of end-stage kidney disease.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)-[1,1'-biphenyl]-2-sulfonamide may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate an improvement of renal function through an alternative mode of action to currently approved medicines. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4'-[(2-butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl)methyl]-N-(4,5-dimethyl-3-isoxazolyl)-2'-(ethoxymethyl)-[1,1'-biphenyl]-2-sulfonamide, for treatment of focal segmental glomerulosclerosis , was adopted by consensus.

2.1.9. Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor - EMA/OD/107/15

Kite Pharma UK, Ltd; Treatment of acute lymphoblastic 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 is asked to re-address the prevalence of the proposed condition in the EU, taking into account the "Points to consider on the calculation and reporting of the prevalence of a condition for orphan designation (COMP/436/01). There it is stated:

"In many situations, the true prevalence at the time of applications will not be known and the demonstration of the 'prevalence criterion' will be based on the estimated prevalence of the condition at a certain point in time. Where this is the case, there should be reasonable evidence that the estimate provided is a good approximation of the true prevalence of the claimed orphan condition in the European Union, at the time of application."

Therefore, the sponsor is asked to critically review and discuss the following aspects:

- Significant sources of bias for any extrapolation should be taken into account, e.g. due to the data collection process into cancer registries, or the impact of the delay between data collection, publication and the time of application.
- Sensitivity analyses on critical assumptions are expected.

In the written response, the sponsor provided a revised prevalence calculation taking into consideration the increased survival seen in children and adults due the increased number of new products being introduced since the first designations.

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

The intention to treat the condition with the medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor was considered justified based on preliminary clinical data showing complete and partial response in patients with the condition.

The condition is life-threatening due to invasion by the tumour cells of the bloodstream and the bone marrow, resulting in lack of normal blood cells, bone marrow failure, and specific organ damage. The condition can be fatal in a few weeks if left untreated.

The condition was estimated to be affecting approximately 1.7 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 have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous T cells transduced with

retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a complete or partial response in relapsed or refractory patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor, for treatment of acute lymphoblastic leukaemia, was adopted by consensus.

2.1.10. Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor - EMA/OD/108/15

Kite Pharma UK, Ltd; Treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma

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 is asked to re-address the prevalence of the proposed condition in the EU, taking into account the "Points to consider on the calculation and reporting of the prevalence of a condition for orphan designation (COMP/436/01). There it is stated:

"In many situations, the *true* prevalence at the time of applications will not be known and the demonstration of the 'prevalence criterion' will be based on the estimated prevalence of the condition at a certain point in time. Where this is the case, there should be reasonable evidence that the estimate provided is a good approximation of the true prevalence of the claimed orphan condition in the European Union, at the time of application."

Therefore, the sponsor is asked to critically review and discuss the following aspects:

- Impact of the recent change in classification with respect to the coding of the condition in the literature or registries referred to.
- Impact of the increasing survival of patients with the proposed condition due to improvements in treatment outcomes, especially in the last decade.
- Significant sources of bias for any extrapolation should be taken into account, e.g. due to the data collection process into cancer registries (coded as leukaemia or lymphoma?), or the impact of the delay between data collection, publication and the time of application, also in view of the potential temporal variation expected to occur due to an ageing and/or growing population in the EU.
- The sponsor is also asked to clarify the proportion of patients diagnosed with CLL/SLL who do not require treatment during the entire disease course.
- Sensitivity analyses on critical assumptions are expected.

In the written response, the sponsor provided an amended prevalence calculation to reflect the increase in the survival of patients with this condition.

The Committee agreed that the condition, treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor was considered justified based on preliminary clinical data showing response in patients with the condition.

The condition is life-threatening and chronically debilitating due to development of cytopenias (anaemia, neutropenia, thrombocytopenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections.

The condition was estimated to be affecting approximately 4.9 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 T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate a response in patients who are relapsed or refractory. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor, for treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma, was adopted by consensus.

2.1.11. Azacitidine - EMA/OD/098/15

Celgene Europe Limited; Treatment nasopharyngeal carcinoma

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

After reviewing the application the committee would like the sponsor to broaden the condition to head and neck cancer. The committee was of the opinion that nasopharyngeal carcinoma shares features of this broader condition and might not be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation; your attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

The sponsor is invited to update the prevalence calculation to encompass the broader proposed condition namely head and neck cancer as this would be taking into consideration the suggested broader condition.

The sponsor should justify the inclusion/choice of the epidemiological index used (5-year partial prevalence) instead of point prevalence in line with the above mentioned guidance document.

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

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 did not endorse the proposal of the COMP and proposed a new subset of NPC, namely "Treatment of head and neck tumours originating in the nasopharynx, WHO classification 2b (undifferentiated, non-keratinizing histology, EBV associated)". Celgene is proposing this indication based on the so-far observed clinical activity. As regards the prevalence calculations, the sponsor did not justify 5 year prevalence vis a vis the complete point prevalence, and further acknowledged that the overall head and neck cancer exceeds the statutory orphan threshold.

The COMP rejected the newly proposed indication, based on the absence of justification of activity outside this subject. However, the underlying population of "nasopharyngeal carcinoma" was considered as a distinct medical entity based on literature references and accepted for the purpose of this application.

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

The intention to treat the condition with the medicinal product containing azacitidine was considered justified based on preliminary clinical data in patients affected by the condition, who responded to treatment with regards to tumour size.

The condition is chronically debilitating in particular due to epistaxis, obstruction of the nasopharynx, hearing impairment and tinnitus, headache, diplopia, facial pain and numbness or paresthesia; the condition is also life-threatening with 5-year survival rates reported less than 10% for patients with stage IVC.

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 azacitidine may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate responses in tumour size in subjects with advanced relapsed or refractory nasopharyngeal carcinoma, who had previously received other therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for azacitidine, for treatment of nasopharyngeal carcinoma, was adopted by consensus.

2.1.12. Pentetrazol - EMA/OD/097/15

Dr Jens Steinbrink; Treatment of idiopathic hypersomnia

COMP coordinator: Josep Torrent-Farnell

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

- Number of people affected

The sponsor has provided a prevalence calculation for a new condition where the assumptions appear to be unclear thereby raising concern regarding the proposed final calculation.

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

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

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 cited a previous designation for narcolepsy (discussing a narcolepsy prevalence of approximately 4 in 10,000), and defended the methodology of indirect prevalence calculation from the IH/narcolepsy ratio, based on paucity of other epidemiological data.

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

The intention to treat the condition with the medicinal product containing pentetrazol was considered justified based on preliminary clinical data in patients affected by the condition where treatment resulted in improvement of symptoms.

The condition is chronically debilitating due to episodes of excessive daytime sleepiness.

The condition was estimated to be affecting approximately 3 in 10,000 persons in the European Union, at the time the application was made; thus, the requirements under Article 3(1)(a) of Regulation (EC) No 141/2000 on orphan medicinal products are fulfilled.

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 pentetrazol, for treatment of idiopathic hypersomnia, was adopted by consensus.

2.1.13. Recombinant human interleukin-3 truncated diphtheria toxin fusion protein - EMA/OD/064/15

Spector Consulting SAS; Treatment of blastic plasmacytoid dendritic cell neoplasm

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

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 current prevalence calculation is based on assumptions from one study from one single centre in Spain, while the other collected published evidence on prevalence from a systemic literature search have been disregarded.

The sponsor is invited to revisit the current prevalence estimate by taking into consideration all the identified published sources, relevant epidemiological studies and registers. It was noted that orphanet and previous COMP designations are not considered to be relevant epidemiological reference sources.

Furthermore, the sponsor is invited to provide a discussion on how the presented prevalence calculation can be used to conclude on a prevalence estimate that is sufficiently valid across the European Union.

In the written response, the sponsor presented a comprehensive literature search but disregarded most of the findings with the reasoning that the reference population had not been provided in most of these reports. The sponsor kept the original methodology based on a single study which was used to establish the proportion of patients with the condition from all previously diagnosed NHL and AML patients. This approach relied on data from only one member state, but there is no evidence that prevalence across Europe varies extensively. Based on this assumption, the sponsor re-calculated AML prevalence taking RARECARE estimates into consideration.

The Committee agreed that the condition, treatment of blastic plasmacytoid dendritic cell neoplasm, 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 interleukin-3 truncated diphtheria toxin fusion protein was considered justified based on preliminary clinical data demonstrating patient responses to treatment.

The condition is life-threatening due to the aggressive progression leading to a mean survival of 12-14 months and overall survival rates of 75-52% after one year.

The condition was estimated to be affecting approximately 1.2 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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for recombinant human interleukin-3 truncated diphtheria toxin fusion protein, for treatment of blastic plasmacytoid dendritic cell neoplasm, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1. (5S,8S,10aR)-N-benzhydryl-5-((S)-2-(methylamino)propanamido)-3-(3-methylbutanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide - EMA/OD/126/15

ASPHALION, SL; Treatment of ovarian cancer

COMP coordinator: Brigitte Bloechl-Daum

The Committee agreed that the condition, treatment of 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 (5S,8S,10aR)-N-benzhydryl-5-((S)-2-(methylamino)propanamido)-3-(3-methylbutanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide was considered justified based on preclinical data showing antitumor efficacy of the proposed product.

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 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 (5S,8S,10aR)-N-benzhydryl-5-((S)-2-(methylamino)propanamido)-3-(3-methylbutanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing increased effect when the product was used in combination with some of the currently authorized treatments for the condition. The Committee considered that this could translate into a clinically relevant advantage for the patients affected by ovarian cancer.

A positive opinion for (5S,8S,10aR)-N-benzhydryl-5-((S)-2-(methylamino)propanamido)-3-(3-methylbutanoyl)-6-oxodecahydropyrrolo[1,2-a][1,5]diazocine-8-carboxamide, for treatment of ovarian cancer, was adopted by consensus.

2.2.2. - EMA/OD/147/15

Treatment of gastric neuroendocrine tumours

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 November meeting.

2.2.3. - EMA/OD/128/15

Treatment of activated PI3Kdelta syndrome (APDS); p110delta-activating mutation causing senescent T Cells, lymphadenopathy and immunodeficiency (PASLI)

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 November meeting.

2.2.4. - EMA/OD/131/15

Prevention 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 November meeting.

2.2.5. Adeno-associated vector serotype 8 encoding the human ATP7B cDNA placed under the control of the human liver-specific α1-anti-trypsin promoter - EMA/OD/114/15

Aligen Therapeutics S.L.; Treatment of Wilson's disease

COMP coordinator: Kerstin Westermark

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 8 encoding the human ATP7B gene under the control of the human alpha-1 antitrypsin promoter was considered justified based on preclinical *in vivo* data from studies in a relevant disease model that demonstrate that treatment enhances hepatic function, reduces hepatic histopathology, normalises serum holoceruloplasmin, decreases copper accumulation in urine and liver, and restores physiologic biliary secretion of copper.

The condition is chronically debilitating and can be life-threatening due to the toxic effects of copper, first accumulating in the liver and later on in the brain. The liver disease can present with symptoms ranging from mildly elevated transaminases to acute liver failure or liver cirrhosis. Around 5% of all patients are diagnosed only when they develop fulminant acute liver failure, sometimes fatal.

The condition was estimated to be affecting approximately 0.6 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing adeno-associated viral vector serotype 8 encoding the human *ATP7B* gene under the control of the human alpha-1 antitrypsin promoter may be of significant benefit to those affected by the condition. The sponsor has provided preclinical *in vivo* data that support a novel mechanism of action of the proposed product that enables the physiological elimination of copper through the biliary system thereby reducing copper excess in urine and liver and restoring hepatic function and histopathology. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for adeno-associated viral vector serotype 8 encoding the human *ATP7B* gene under the control of the human alpha-1 antitrypsin promoter, for treatment of Wilson's disease, was adopted by consensus.

2.2.6. Adenovirus associated viral vector serotype 5 containing the human *RPE65* gene - EMA/OD/129/15

Athena Vision Ltd; Treatment of Leber congenital amaurosis

COMP coordinator: Armando Magrelli

The Committee agreed that the condition, treatment of Leber's congenital amaurosis, 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 5 containing the human RPE65 gene was considered justified based on preliminary clinical data in patients of the condition showing improvements in retinal sensitivity and vision guided navigation.

The condition is chronically debilitating due to loss of visual acuity.

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.

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 adenovirus associated viral vector serotype 5 containing the human *RPE65* gene, for treatment of Leber's congenital amaurosis, was adopted by consensus.

2.2.7. Adenovirus associated viral vector serotype 8 containing the human CNGB3 gene - EMA/OD/130/15

Alan Boyd Consultants Ltd; Treatment of Achromatopsia

COMP coordinator: Armando Magrelli

The Committee agreed that the condition, treatment of achromatopsia caused by mutations in the *CNGB3* gene, 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 CNGB3 gene was considered justified based on preclinical data showing long-term cone survival and improved visual acuity.

The condition is chronically debilitating due to loss of colour vision, reduced visual acuity, nystagmus and disabling photophobia.

The condition was estimated to be affecting 0.15 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 adenovirus associated viral vector serotype 8 containing the human CNGB3 gene, for treatment of achromatopsia caused by mutations in the CNGB3, was adopted by consensus.

2.2.8. - EMA/OD/094/15

Treatment of Primary Sjogren'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 November meeting.

2.2.9. Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor - EMA/OD/135/15

Kite Pharma EU B.V.; Treatment of follicular lymphoma

COMP coordinator: Frauke Naumann-Winter

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

The intention to treat the condition with the medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor was considered justified based on preliminary clinical data showing a response in relapsed/refractory patients.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation to aggressive lymphoma.

The condition was estimated to be affecting approximately 2.8 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that remission was recorded in relapsed and refractory patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor, for treatment of follicular lymphoma, was adopted by consensus.

2.2.10. - EMA/OD/263/14

Treatment of myotonic dystrophy

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 November meeting.

2.2.11. - EMA/OD/144/15

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 November meeting.

2.2.12. - EMA/OD/106/15

Treatment of ascites

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 November meeting.

2.2.13. Humanised monoclonal antibody of the IgG4 kappa isotype targeting CD47 - EMA/OD/145/15

University of Oxford; Treatment of acute myeloid leukaemia

COMP coordinator: Karri Penttila

The Committee agreed that the condition, treatment of 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 humanised monoclonal antibody of the IgG4 kappa isotype targeting CD47 was considered justified based on pre-clinical *in vivo* data showing tumour reduction and improved survival.

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 within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%.

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 humanised monoclonal antibody of the IgG4 kappa isotype targeting CD47 may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical *in vivo* data that demonstrate a reduction in leukaemic cells and improved survival. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for humanised monoclonal antibody of the IgG4 kappa isotype targeting CD47, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.14. - EMA/OD/137/15

Treatment of adrenal insufficiency

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 November meeting.

2.2.15. - EMA/OD/099/15

Treatment of gastric 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 November meeting.

2.2.16. - EMA/OD/127/15

Treatment of amyotrophic lateral sclerosis

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

2.2.17. - EMA/OD/138/15

Treatment of cystic fibrosis

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

2.2.18. - EMA/OD/125/15

Prevention of mercury toxicity

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 November meeting.

2.2.19. - EMA/OD/154/14

Treatment of Wilson's 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 November meeting.

2.2.20. N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4 methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide - EMA/OD/136/15

Pharma Gateway AB; Treatment of neuroblastoma

COMP coordinator: Daniel O'Connor

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

The intention to treat the condition with the medicinal product containing N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4 methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide was considered justified based on preclinical *in vivo* data in a valid disease model showing reduction in tumour volume upon treatment, and preliminary clinical response to treatment in one patient.

The condition is life threatening and chronically debilitating due to its aggressive nature and frequency of metastatic disease. It accounts for almost 15% of childhood cancer fatalities. The likelihood of survival is dependent on the age of the patient, the stage and biological characteristics of the disease. The poorest prognosis is seen in children diagnosed at older age (>15 months), those diagnosed at later stages of disease, and those positive for certain molecular biological markers such as myelocytomatosis viral related oncogene-Neuroblastoma derived (MYCN) amplification, which occurs in 5–10% of cases in infants up to 1 year and in 20–30% of childhood and adolescent cases.

The condition was estimated to be affecting approximately 1.1 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 N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4 methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide may be of significant benefit to those affected by the condition. The sponsor has provided preclinical

data that demonstrate that treatment on top of existing chemotherapeutic agents results in a synergistic antineoplastic effect on tumour volume. Furthermore, preliminary clinical data have been presented that show a response to treatment in patients refractory to other currently available treatment options. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-[5-(3,5-difluorobenzyl)-1H-indazol-3-yl]-4-(4 methylpiperazin-1-yl)-2-(tetrahydro-2H-pyran-4-ylamino)benzamide, for treatment of neuroblastoma, was adopted by consensus.

2.2.21. - EMA/OD/133/15

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 November meeting.

2.2.22. - EMA/OD/095/15

Treatment of short bowel 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 November meeting.

2.2.23. - EMA/OD/143/15

Treatment of neurotrophic keratitis

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 November meeting.

2.2.24. - EMA/OD/142/15

Treatment of beta-thalassemia intermedia and major

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 November meeting.

2.2.25. Sodium phenylbutyrate - EMA/OD/141/15

Fondazione Telethon; Treatment of pyruvate dehydrogenase complex deficiency

COMP coordinator: Ingeborg Barisic

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

The intention to treat the condition with the medicinal product containing sodium phenylbutyrate was considered justified based on preclinical data showing improved locomotor activity and a reduction in lactate and pyruvate levels.

The condition is life-threatening due to lactic acidosis, respiratory failure and infections, and chronically debilitating due to progressive neurological degeneration, elevation of lactate in blood and cerebrospinal fluid.

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 that has been authorised in the European Union for patients affected by the condition.

A positive opinion for sodium phenylbutyrate, for treatment of pyruvate dehydrogenase complex deficiency, was adopted by consensus.

2.2.26. - EMA/OD/140/15

Treatment of Duchenne muscular dystrophy

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 November meeting.

2.2.27. - EMA/OD/139/15

Treatment of primary sclerosing cholangitis

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 November meeting.

2.3. Revision of the COMP opinions

None.

2.4. COMP opinions adopted via written procedure following previous meeting

None.

2.5. Appeal

None.

2.6. Nominations

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

COMP coordinators were appointed for 15 applications submitted and 15 upcoming applications.

2.7. Evaluation on-going

The Committee noted that evaluation was on-going for 23 applications for orphan designation.

3. Requests for protocol assistance with significant benefit question

3.1. Ongoing procedures

3.1.1. -

Treatment of sickle cell disease

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 systemic 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 acromegaly

The Committee was briefed on the significant benefit issues.

[*Post-meeting note: The COMP adopted the proposed answers on the significant benefit issues via written procedure on 12 October 2015.]*

3.1.4. -

Treatment of glycogen storage disease type II (Pompe's disease)

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

3.1.5. -

Treatment of Prader-Willi syndrome

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

3.2. Finalised letters

None.

3.3. New requests

3.3.1. -

Treatment of ovarian cancer

The new request was noted.

3.3.2. -

Treatment of amyotrophic lateral sclerosis

The new request was noted.

3.3.3. -

Treatment of growth hormone deficiency

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

4.1.1. Elocta - efmoroctocog alfa – EMA/OD/030/10, EU/3/10/783, EMEA/H/C/003964

Biogen Idec Ltd; Treatment of haemophilia A

COMP coordinators: Armando Magrelli and Karri Penttilä

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

- Significant benefit

The sponsor is assuming significant benefit of the proposed product based on PK data from the pivotal trials showing longer half-life than some of the currently authorized products for the condition, in particular Advate, which is authorized for the same indication as the proposed product.

However for confirmation of significant benefit at marketing authorization the potential advantage from a different PK profile should be demonstrated to translate into a measured clinically relevant advantage or major contribution to patient care for the patients affected by the condition.

The sponsor is therefore invited to discuss any available data supporting the clinically relevant advantage or major contribution to patient care with the proposed product.

In its written response, and during an oral explanation before the Committee on 6 October 2015, the sponsor discussed the longer half-life of the product compared to conventional factor VIII replacement therapies, which directly results in a reduction of the number of injections in patients who are on prophylaxis treatment. The burden was expected to be of a magnitude of 40 up to 100 fewer injections per year for adults and adolescents and 40 to 80 fewer injections for children. In turn this reduction was expected to result in improved adherence to prophylaxis, and fewer injection-related complications.

Patient representatives were also invited by the EMA to participate in the meeting, and testified their experiences with regards to the difficulties encountered with the administration of factor VIII containing products.

The COMP acknowledged the reduction of the number of injections, but pointed out that no data have been presented with regards to the consequences of such a reduction, such as quality of life improvements, or improvements with regards to adherence to treatment. Without data to justify the claim of major contribution to patient care, the significant benefit criterion could not be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 7 October 2015, prior to final opinion.

4.1.2. Kyprolis - carfilzomib – EMEA/OD/120/07, EU/3/08/548, EMEA/H/C/003790

Amgen Europe B.V.; Treatment of multiple myeloma

COMP coordinators: Karri Penttilä and Jens Ersbøll

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

- Number of people affected

The sponsor is requested to recalculate the prevalence of the proposed condition, taking into consideration the recent advancements in the prognosis of the proposed condition that would result in an increase of the duration of the proposed condition.

For the calculation and presentation of the prevalence data it 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

The sponsor is invited to further elaborate on the justification of significant benefit taking into consideration the CHMP therapeutic indication.

A discussion in particular with regards to bortezomib, pomalidomide and panobinostat is expected. Any historical/bibliographical comparisons presented would have to address the comparability of the populations, design, treatments and results of those studies.

Furthermore, any existing data from the ongoing study comparing directly the two proteasome inhibitors in the context of the condition should be presented to the COMP.

In its written response, and during an oral explanation before the Committee on 6 October 2015, the sponsor further elaborated on the issues raised.

With regards to the prevalence issue and for the requested analysis the sponsor assumed a five-year duration and took also into consideration the crude incidence rate from GLOBOCAN sources. Based on this the sponsor revises upwards the prevalence up to 3.3 per 10,000.

Regarding significant benefit, authorised products with an indication in this particular setting (second line) were bortezomib, doxorubicin and lenalidomide.

Starting with bortezomib the sponsor provided new head to head data from a study designed to demonstrate superiority in PFS of carfilzomib to bortezomib when each was administered in combination with dexamethasone. Subjects in the carfilzomib (Kyprolis) plus dexamethasone arm had a clinically significant improvement in PFS that represented a

doubling of that experienced by subjects in the bortezomib plus dexamethasone (18.7 months vs. 9.4 months).

With regards to doxorubicin, it has been authorised in combination with bortezomib, and the sponsor performed an indirect comparison versus the marketing authorisation study. The latter involved subjects who had received at least 1 prior therapy and who did not progress while receiving anthracycline-based therapy and were treated with either doxorubicin in combination with bortezomib or with bortezomib alone. Progression-free survival was a secondary endpoint for the study. The median PFS was 9.0 months for doxorubicin with bortezomib compared with 6.5 months for bortezomib alone. These PFS results are lower compared to the study of carfilzomib (PFS was 26.3 months in the CRd arm versus 17.6 months in the Rd arm).

As for lenalidomide, it is authorised for the treatment of adult patients with previously untreated multiple myeloma, who are not eligible for transplant, but also in combination with dexamethasone for the treatment of multiple myeloma in adult patients who have received at least one prior therapy. The sponsor presented a comparative table (a juxtaposition of pivotal studies) where PFS for lenalidomide plus dexamethasone was 11.1 months, versus 4.6 of dexamethasone alone. This 11.1 month when indirectly compared to the PFS of the ASPIRE study, (26.3 months for the KRd arm) also supports the significant benefit issue.

The COMP was of the opinion that based on the head to head data showing improved efficacy versus bortezomib, and indirect comparisons with regards to PFS versus the other two products authorised for second line, the criterion of significant benefit had been justified.

The COMP concluded that:

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

The prevalence of multiple myeloma (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be approximately 3.3 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The proposed condition is chronically debilitating in particular due to the development of hypercalcemia, renal insufficiency, anaemia and bone lesions, and life-threatening with an overall survival of up to approximately 6 years.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Kyprolis may be of potential significant benefit to those affected by the orphan condition still holds.This was based on data comparing directly the efficacy of the product versus bortezomib and as a combination with lenalidomide**,** as well as indirect comparisons versus doxorubicin, showing improved progression free survival in patients who have received at least one prior treatment.

An opinion not recommending the removal of Kyprolis, carfilzomib (EU/3/08/548) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion was adopted for publication on the EMA website.

4.1.3. Orkambi - lumacaftor / ivacaftor – EMA/OD/032/14, EU/3/14/1333, EMEA/H/C/003954

Vertex Pharmaceuticals (U.K.) Ltd.; Treatment of cystic fibrosis

COMP coordinators: Josep Torrent-Farnell and Armando Magrelli

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

In order to justify the significant benefit of the proposed product the sponsor is invited to further elaborate on the clinically relevant advantage provided by the proposed product for the patients affected by cystic fibrosis.

This would also include providing details on the standard of care of the patients of the pivotal trials, with discussion on the clinical relevance of the changes induced by the proposed product on top of such standard of care.

In its written response, and during an oral explanation before the Committee on 6 October 2015, the sponsor further elaborated on the issue of significant benefit. The applicant stressed that the combination therapy of lumacaftor/ivacaftor has been specifically developed to target the underlying cause of CF in patients homozygous for the F508del. The sponsor also discussed the standard of care received in the pivotal Phase 3 Studies with most commonly-used concomitant medications being dornase alfa, pancreatin, salbutamol, sodium chloride, antibiotics, and Seretide. The results of the pivotal studies in particular with regards to FEV1 and exacerbations were also discussed.

The COMP considered that the results from the pivotal studies, even though statistically significant, would not be clinically relevant to such an extent, as to justify a clinically relevant advantage for the purpose of significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the orphan designation from the register of orphan medicinal products, on 7 October 2015, prior to final opinion.

4.1.4. Blincyto – blinatumomab - EMA/OD/029/09, EU/3/09/650, EMEA/H/C/003731

Amgen Europe B.V.; Treatment of acute lymphoblastic leukaemia

COMP coordinators: Jens Ersbøll and Karri Penttilä

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

ALL is the most common type of cancer in children, with more preferable prognosis than in adults (for example in UK, in those aged 14 or younger the 5-year survival rate is more than 90% compared to 40% in those aged between 25 and 64).

In addition to Philadelphia chromosome positivity (app. 20-25% in adult ALL patients), there are other chromosomal abnormalities with poor prognosis in adults. On the other hand, Philadelphia chromosome positivity is rare in children (app. 3-4% in childhood ALL patients).

The sponsor should further elaborate on the relevance of the clinical Phase II studies submitted to support the claim that their product offers a clinically relevant advantage in the target patient ALL population.

In its written response, and during an oral explanation before the Committee on 6 October 2015, the sponsor further elaborated on the population, previous treatments and results of the key pivotal study in support of the marketing authorisation application. All patients were diagnosed with relapsed/refractory Philadelphia (Ph)-negative ALL and it was particularly noted that 80% of patients received blinatumomab as third-line therapy or later, 34% of patients had relapsed after prior HSCT and 5.3% of failed 2 prior allogeneic HSCTs. In addition, a retrospective analysis showed that 55.5% of patients had not achieved remission with their last line of therapy. In this patient population, the complete remission/complete remission with partial haematological recovery was reported to be 42.9% and median overall survival of 6.1 months. The sponsor also performed an historical comparison versus pooled data from many groups across the EU and US, supporting improved outcomes versus the pivotal study of the product.

The COMP concluded that:

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

The prevalence of acute lymphoblastic leukaemia (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 1.8 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening particularly due to the poor long-term prognosis if the disease relapses after systemic therapy.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Blincyto may be of potential significant benefit to those affected by the orphan condition has been justified with clinical data showing the effectiveness in patients who are negative for the Philadephia gene and for whom there is no effective treatment.

An opinion not recommending the removal of Blincyto, blinatumomab (EU/3/09/650) from the EC Register of Orphan Medicinal Products was adopted by consensus.

[*Post-meeting note: The draft public summary of the COMP opinion was adopted via written procedure on 14 October 2015 for publication on the EMA website.]*

4.1.5. RAVICTI - glyceryl tri-(4-phenylbutyrate) – EMEA/H/C/003822

Horizon Therapeutics Limited;

COMP coordinators: Annie Lorence and Vallo Tillmann

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EMA/OD/124/09, EU/3/10/733)

The COMP concluded that:

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

The prevalence of carbamoyl-phosphate synthase-1 deficiency (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 0.14 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 the consequences of metabolic disturbance that leads to intellectual disability and other types of neurological damage. The life threatening nature is justified by the overall shorter survival associated with the condition.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Ravicti may be of potential significant benefit to those affected by the orphan condition has been supported by data showing that the frequency of hyperammonaemia crisis was much lower to those achieved with current treatments as well as the acceptability in paediatric patients.

An opinion not recommending the removal of RAVICTI - Glyceryl tri-(4-phenylbutyrate) (EU/3/10/733) from the EC Register of Orphan Medicinal Products was adopted by consensus.

b) treatment of ornithine carbamoyltransferase deficiency (EMA/OD/002/10, EU/3/10/734)

The COMP concluded that:

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

The prevalence of ornithine carbamoyltransferase deficiency (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 0.14 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 the consequences of metabolic disturbance that leads to intellectual disability and other types of neurological damage. The life threatening nature is justified by the overall shorter survival associated with the condition.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Ravicti may be of potential significant benefit to those affected by the orphan condition has been supported by data showing that the frequency of hyperammonaemia crisis was much lower to those achieved with current treatments as well as the acceptability in paediatric patients.

An opinion not recommending the removal of RAVICTI - Glyceryl tri-(4-phenylbutyrate) (EU/3/10/734) from the EC Register of Orphan Medicinal Products was adopted by consensus.

c) treatment of citrullinaemia type 1 (EMA/OD/003/10, EU/3/10/735)

The COMP concluded that:

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

The prevalence of citrullinaemia type 1 (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 0.2 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 the consequences of metabolic disturbance that leads to intellectual disability and other types of neurological damage. The life threatening nature is justified by the overall increased mortality rate associated with the condition.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Ravicti may be of potential significant benefit to those affected by the orphan condition has been supported by data showing that the frequency of hyperammonaemia crisis was much lower to those achieved with current treatments as well as the acceptability in paediatric patients.

An opinion not recommending the removal of RAVICTI - Glyceryl tri-(4-phenylbutyrate) (EU/3/10/735) from the EC Register of Orphan Medicinal Products was adopted by consensus.

d) treatment of argininosuccinic aciduria (EMA/OD/004/10, EU/3/10/736)

The COMP concluded that:

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

The prevalence of argininosuccinic aciduria (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be 0.06 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 the consequences of metabolic disturbance that leads to intellectual disabilities and other types of neurological damage. The life threatening nature is justified by the overall increased mortality rate associated with the condition.

There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition

An opinion not recommending the removal of RAVICTI - Glyceryl tri-(4-phenylbutyrate) (EU/3/10/736) from the EC Register of Orphan Medicinal Products was adopted by consensus.

e) treatment of hyperargininaemia (EMA/OD/005/10, EU/3/10/737)

The COMP concluded that:

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

The prevalence of hyperargininaemia (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be 0.03 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 the consequences of metabolic disturbance that leads to intellectual disability and other types of neurological damage. The life threatening nature is justified by the overall increased mortality rate associated with the condition.

There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

An opinion not recommending the removal of RAVICTI - Glyceryl tri-(4-phenylbutyrate) (EU/3/10/737) from the EC Register of Orphan Medicinal Products was adopted by consensus.

f) treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) (EMA/OD/006/10, EU/3/10/738)

The COMP concluded that:

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

The prevalence of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 and was concluded in to be 1.2 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 the consequences of metabolic disturbance that leads to intellectual disability and other types of neurological damage. The life threatening nature is justified by the overall increased mortality risk associated with the condition.

There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition

An opinion not recommending the removal of RAVICTI - Glyceryl tri-(4-phenylbutyrate) (EU/3/10/738) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinions was adopted for publication on the EMA website.

4.1.6. Kolbam - cholic Acid - EMEA/OD/080/09, EU/3/09/683, EMEA/H/C/002081

Retrophin Europe Ltd, treatment of inborn errors of primary bile acid synthesis responsive to treatment with cholic acid

COMP coordinator: Armando Magrelli

COMP position adopted on 6 February 2014, was revised on 8 October 2015.

The COMP concluded that:

The proposed therapeutic indication "treatment of inborn errors in primary bile acid synthesis due to Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency or Cholesterol 7α-hydroxylase (CYP7A1) deficiency in infants, children and adolescents aged 1 month to 18 years and adults" falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product which is worded at broader terms as: "treatment of inborn errors in primary bile acid synthesis responsive to treatment with cholic acid".

The prevalence of inborn errors of primary bile acid synthesis responsive to treatment with cholic acid is estimated to remain below 5 in 10,000 at the time of the review of the designation criteria, and in particular to be affecting approximately 0.06 per 10,000 people in the EU at the time of the review.

The condition is chronically debilitating and life-threatening in particular due to the development of liver failure and cirrhosis. If untreated, the condition leads to death within 2-3 years.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification that the medicinal product containing cholic acid is of significant benefit to those affected by the condition. This is justified because the product is indicated for specific enzyme deficiencies, which are different to the enzyme deficiencies targeted by the authorised product. The Committee considered that this constitutes a clinically relevant advantage.

An opinion not recommending the removal of Kolbam (cholic acid) (EU/3/09/683) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinions was adopted for publication on the EMA website.

4.1.7. Obizur - susoctocog alfa – EMEA/H/C/002792, EMA/OD/043/10, EU/3/10/784

Baxalta Innovation GmbH; Treatment of haemophilia A

COMP coordinator: Karri Penttilä; CHMP rapporteur: Greg Markey; CHMP co-rapporteur: Outi Mäki-Ikola

COMP position adopted on 3 September 2015, was revised on 8 October 2015.

The COMP concluded that:

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

The prevalence of haemophilia A (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be approximately 0.7 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 spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury. Approximately 80-85% of bleeding episodes occur in the muscles and joints of the elbows, knees and ankles, causing acute haemarthrosis and synovitis. Recurrent bleeds in the same location lead to chronic arthropathy, muscular atrophy and deformities. In young children with severe haemophilia, spontaneous bleeds occur within the first 2 years of life, after the child starts to walk. Rare but life-threatening bleeds also occur in the central nervous system, throat, neck, and gastrointestinal tract.

In relation to the existence of satisfactory methods of treatment of the condition that are authorised in the European Union, the assumption that Obizur is of significant benefit to those affected by the orphan condition is not confirmed. An indirect comparison was performed by the sponsor between their case-series clinical study and literature studies for the authorised products for the specific therapeutic indication, namely prothrombin complex concentrates and activated FVII; this comparison did not confirm improved efficacy or safety; moreover the argued potential for improved titration and monitoring that was proposed by the sponsor was not supported by data with regards to leading to improved bleeding control. The COMP concluded that the sponsor did not justify a clinically relevant

advantage or major contribution to patient care over the existing methods of treatment for the proposed indication.

An opinion recommending the removal of Obizur, recombinant porcine factor VIII (B domain deleted), susoctocog alfa (EU/3/10/784) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

4.2.1. Heparesc - human heterologous liver cells - EMEA/H/C/003750

Cytonet GmbH&Co KG;

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EMA/OD/108/10, EU/3/10/821)

b) treatment of ornithine-transcarbamylase deficiency (EMEA/OD/042/07, EU/3/07/470)

c) treatment of citrullinaemia type 1 (EMA/OD/105/10, EU/3/10/818)

d) treatment of hyperargininaemia (EMA/OD/106/10, EU/3/10/819)

e) treatment of argininosuccinic aciduria (EMA/OD/107/10, EU/3/10/820)

Status of the procedure at CHMP was noted.

4.2.2. Revlimid – lenalidomide - Type II variation - EMA/OD/078/11, EU/3/11/924, EMEA/H/C/000717/II/0079

Celgene Europe Limited; Treatment of mantle cell lymphoma

CHMP rapporteur: Pierre Demolis; CHMP co-rapporteur: Filip Josephson

The sponsor will be invited to an oral explanation before the Committee at the November meeting.

[*Post-meeting note: The COMP adopted a list of issues via written procedure on 14 October 2015 that was sent to the sponsor.*]

4.2.3. Wakix - 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride - EMEA/OD/087/06, EU/3/07/459, EMEA/H/C/002616

Bioprojet; Treatment of narcolepsy

The sponsor will be invited to an oral explanation before the Committee at the November meeting.

[Post-meeting note: The COMP adopted a list of issues via written procedure on 14 October 2015 that was sent to the sponsor.]

4.2.4. Spectrila - asparaginase – EMA/OD/063/04, EU/3/04/258, EMEA/H/C/002661

Medac Gesellschaft fuer klinische Spezialpraeparate mbH; Treatment of acute lymphoblastic leukaemia

The sponsor will be invited to an oral explanation before the Committee at the November meeting.

[*Post-meeting note: The COMP adopted a list of issues via written procedure on 14 October 2015 that was sent to the sponsor.*]

4.3. On-going procedures

4.3.1. List of on-going procedures

COMP co-ordinators were appointed for 3 applications.

5. Organisational, regulatory and methodological matters

5.1. Mandate and organisation of the COMP

5.1.1. Strategic Review & Learning meetings

COMP/PDCO Strategic Review & Learning Meeting under the Luxembourg Presidency to be held on 15-16 October 2015 in Bonn

The agenda of the joint COMP/PDCO Strategic Review & Learning Meeting to be held in Bonn was presented to the COMP. The COMP agreed on the proposed agenda.

COMP/CHMP Strategic Review & Learning Meeting under the Netherlands Presidency to be held on 31 May – 1 June 2016 in Utrecht

COMP was informed about the next Strategic Review & Learning Meeting.

Strategic Review & Learning Meetings organised during the term of the European Presidency:
- Organisational aspects
- Clarification on responsibility for handling of declared interests and on involvement of external (non NCA) speakers

The general presentation on the Strategic Review & Learning Meetings was postponed to the November COMP meeting.

5.1.2. Election of Chair and Vice-Chair – 6 October 2015

On 6th October 2015, the European Medicines Agency's (EMA's) Committee for Orphan Medicinal Products (COMP) re-elected Professor Bruno Sepodes and Ms Lesley Greene as chair and vice-chair respectively for a second term of three years, beginning this month.

5.1.3. Workshop - Demonstrating significant benefit of orphan medicines - 7 December 2015

The European Medicines Agency (EMA) is organising a workshop on 7 December 2015 to discuss the approach that should be followed by medicine developers to demonstrate the significant benefit of an orphan medicine over existing treatments. Demonstrating a significant benefit is one of the criteria medicines that treat rare diseases must fulfil to benefit from 10 years of market exclusivity once they have been authorised. The workshop

will bring together medicine developers, regulators, healthcare professionals, academia, patients, health-technology-assessment bodies and healthcare payers.

5.2. Coordination with EMA Scientific Committees or CMDh-v

None.

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

5.3.1. Significant Benefit Working Group

The working group on Significant Benefit met on 8 October 2015.

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

None.

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

None.

5.4. Cooperation within the EU regulatory network

5.4.1. European Commission

None.

5.4.2. The European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP)

Dinah Duarte was appointed to represent the COMP at the Steering Group of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

5.4.3. Review of the 2003 Communication on Orphan Medicinal Products

The COMP discussed the draft Revision of the 2003 Communication on orphan medicinal product and agreed on comments to be sent back to EC after the meeting.

5.5. Cooperation with International Regulators

5.5.1. Food and Drug Administration (FDA)

EMA/FDA teleconference on Orphan Medicines – 15 September 2015

The agenda was circulated for information.

5.6. Contacts of the COMP with external parties and interaction with the Interested Parties to the Committee

None.

5.7. COMP work plan

None.

5.8. Planning and reporting

5.8.1. List of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2015

An updated list of all applications submitted/expected and the COMP coordinatorship distribution of valid applications submitted in 2015 were circulated.

5.8.2. Overview of orphan marketing authorisations/applications

An updated overview of orphan applications for Marketing Authorisation was circulated.

5.8.3. Meeting dates

The COMP meeting dates for 2016 were circulated for information.

6. Any other business

6.1. -

6.1.1. –

List of participants

List of participants including any restrictions with respect to involvement of members / experts following evaluation of declared interests for the 6-8 October 2015 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	
André Lhoir	Member	Belgium	No interests declared	
Irena Bradinova	Member	Bulgaria	No interests declared	
Adriana Andrić	Member	Croatia	No interests declared	
Andri Andreou	Member	Cyprus	No interests declared	
Jens Ersbøll	Member	Denmark	No interests declared	
Karri Penttilä	Member	Finland	No interests declared	
Annie Lorence	Member	France	No interests declared	
Nikolaos Sypsas	Member	Greece	No restrictions applicable to this meeting	
Judit Eggenhofer	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	
Aušra Matulevičienė	Member	Lithuania	No interests declared	
Michel Hoffmann	Member	Luxembourg	No interests declared	
Violeta Stoyanova	Member	Netherlands	No interests declared	
Bożenna Dembowska-Bagińska	Member	Poland	No restrictions applicable to this meeting	
Dinah Duarte	Member	Portugal	No interests declared	
Zuzana Batova	Member	Slovak Republic	No interests declared	
Martin Možina	Member	Slovenia	No interests declared	
Josep	Member	Spain	No interests declared	

Name	Role	Member state or affiliation	Outcome restriction following evaluation of e-DoI	Topics on agenda for which restrictions apply
Torrent-Farnell				
Kerstin Westermark	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	
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*	Eurordis	No restrictions applicable to this meeting	
Adrianus Jacobus van IJperen	Expert - in person*	Patient	No restrictions applicable to this meeting	
Brian O'Mahony	Expert - in person*	Patient	No restrictions applicable to this meeting	
A representative from the European Commission attended the meeting				
Meeting run with support from relevant EMA staff				

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