5 March 2014
EMA/COMP/687306/2013
Human Medicines Research and Development Support

Committee for Orphan Medicinal Products (COMP)

Minutes of the 10 - 12 December 2013 meeting

Chair: B. Sepodes – Vice-chair: L. Greene

Note on access to documents

Some documents mentioned in the agenda/minutes cannot be released at present following a request for access to documents under Regulation (EC) No 1049/2001 as they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1 Adoption of the agenda, EMA/COMP/687300/2013

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 5 - 6 November 2013 EMA/COMP/622526/2013 was finalised via written procedure on 18 December 2013.

The minutes were adopted via written procedure on 17 December 2013.

1.3 Conflicts of Interest

The Chair asked the Committee members to declare their potential conflict of interest.

K. Kubackova declared a potential conflict of interest for agenda point 2.2.11.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.8 Allogeneic bone-marrow derived adherent, ex-vivo expanded multipotent adult progenitor cells for prevention of graft-versus-host disease, ReGenesys BVBA - EMA/OD/146/13 *[Co-ordinator: K. Westermark]*

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the prevalence issue. The sponsor was invited to recalculate the estimated population at risk of graft versus host disease taking into account the worst case scenario.

In the written response the sponsor provided estimates of the population at risk starting from current figures of haematopoietic stem cell transplantation in Europe from different sources, including international databases and published literature. The sponsor calculated the population at risk for each single EU member state and provided a final estimate of 0.32 in 10,000. The COMP considered that the methodology used by the sponsor for the prevalence calculation was valid, and the results acceptable. The prevalence estimate was approximated to less than 0.4 in 10,000, taking into account the previous knowledge of the COMP and in line with previous designations.

For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered that allogeneic bone-marrow derived adherent, ex-vivo expanded multipotent adult progenitor cells should be renamed as “allogeneic bone-marrow derived ex-vivo expanded multipotent adult progenitor cells”.

The Committee agreed that the condition, 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 allogeneic bone-marrow derived ex-vivo expanded multipotent adult progenitor cells was considered justified based on preclinical data showing improved survival in models of the condition with the proposed product.

[1] The procedures under assessment discussed by the COMP are considered confidential. COMP meeting reports and subsequent minutes will contain additional details on these procedures once these are finalised. Access to documents in relation to these procedures is possible after marketing authorisation is granted according to the Agency policy on access to documents (EMA/127362/2006).

The condition is chronically debilitating or life-threatening depending on the severity and the response to treatment with corticosteroids and other immunosuppressive agents. The acute forms are characterised mainly by severe intestinal inflammation with diarrhoea, abdominal pain, nausea and vomiting. Severe skin rash is also present, and damage to the mucosa. In the chronic forms also connective tissue and exocrine glands can be affected. Severe infection can occur due to the immunosuppressive agents currently used for the treatment of the condition. Mortality from graft-versus-host disease can reach 100% in the severe forms not responding to immunosuppressive treatment.

The population of patients eligible for prevention of the condition was estimated to be less than 0.4 in 10,000 people in the European Union, at the time the application was made, based on the available literature and on international databases.

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 allogeneic bone-marrow derived ex-vivo expanded multipotent adult progenitor cells may be of significant benefit to the population at risk of developing the condition. The sponsor has provided preclinical data showing improved survival with the proposed product and preliminary clinical data showing less occurrence of severe graft versus host disease. The Committee considered that this constitutes a clinically relevant advantage for the patients at risk of graft-versus-host disease.

A positive opinion for allogeneic bone-marrow derived ex-vivo expanded multipotent adult progenitor cells, for prevention of graft-versus-host disease, was adopted by consensus.

2.1.2 Adenovirus specific T-cells derived from allogeneic donor leukocytes, expanded ex vivo for treatment of adenovirus infection in allogeneic haematopoietic stem cell transplant recipients, Cell Medica Ltd. - EMA/OD/135/13

[Co-ordinator: B. 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:

- Medical plausibility

To establish correctly if there exists a scientific rationale the sponsor was invited to further elaborate on:

- the mechanism of action of the product supported by any available data;

- the relevance of the adenoviral levels monitored in the preliminary clinical study in the context of other concomitant antiviral therapies.

- any available further endpoints studied in the patients in the ongoing trial.

- Significant Benefit

The sponsor was requested to submit a significant benefit justification versus commonly used antiviral compounds in the clinical practice in patients affected by the proposed condition as applied for designation.

In the written response, and during an oral explanation before the Committee on 10 December 2013, the sponsor firstly provided a set of data with regard to the proposed mechanism of action. It was shown that batches of the product contain cells that can be stimulated in vitro by adenoviral peptides

to generate interferon-gamma (measured by ELISPOT and by Intracellular Cytokine Staining methods), to proliferate (by using CFSE staining) and to lyse virus infected cells (phytohemagglutinnin generated blast cells infected with adenovirus).

Furthermore, the sponsor elaborated on the three patients described in the initial application. A more detailed report on the chronological orders of treatments is given and the results observed. The sponsor concluded that "whilst it is difficult to analyse two of the three patients due to concomitant medications and co-morbidities, patient A1/02 has demonstrated that viral clearance correlates with the in vivo presence and expansion of ADV specific T-cells". During the oral presentation, the sponsor also asserted that the concomitant antiviral treatment in these patients would not be expected to result in such a fast drop in viral loads but to only give enough time for the product to act.

Finally, with regards to the significant benefit, the sponsor reiterated that there are no authorised products, so significant benefit is not applicable, but discusses in particular cidifovir that is used of label and presented a short position on improved safety.

The COMP considered that the intention to treat was acceptable and that there exists no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition. A recommendation for seeking protocol assistance was also expressed.

The Committee agreed that the condition, adenovirus infection in allogeneic haematopoietic stem cell transplant recipients, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing adenovirus-specific T-cells derived from allogeneic donor leukocytes, expanded ex vivo was considered justified based on preclinical and preliminary clinical data showing reduction of viral load in treated patients. The condition is chronically debilitating and life-threatening in particular due to the development of interstitial pneumonitis, hepatitis, haemorrhagic cystitis or nephritis, haemorrhagic colitis, encephalitis and disseminated infection.

The condition was estimated to be affecting less than 0.2 in 10,000 people 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-specific T-cells derived from allogeneic donor leukocytes, expanded ex vivo, for treatment of adenovirus infection in allogeneic haematopoietic stem cell transplant recipients, was adopted by consensus.

2.1.3 Product for treatment of plasma cell myeloma - EMA/OD/125/13

[Co-ordinator: K. Kubáčková]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation on 21 November 2013, prior to responding to the list of issues.

2.1.4 Product for prevention of neovascular glaucoma - EMA/OD/130/13

[Co-ordinator: A. Magrelli]

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

The sponsor presents data about the prevalence of NVG among patients with the most common NVG-underlying aetiologies, namely iCRVO and PDR. A corrective factor has been applied to the calculated prevalence to account for the population at high risk of NVG, the use of which has not been sufficiently justified. It also seems that the sponsor has excluded part of the population at risk of the condition, namely patients at risk of NVG with other aetiologies than iCRVO and PDR, i.e. carotid artery obstruction.

The sponsor should substantiate the sources selected for the estimation of the prevalence of the condition, in particular with regard to epidemiological information on NVG due to PDR.

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, and during an oral explanation before the Committee on 10 December 2013, the sponsor clarified that there are several other uncommon causative underlying pathologies that are associated with NVG including ocular ischaemic syndrome, ocular radiation, uveitis, ocular tumours or miscellaneous retinal diseases associated with systemic disease such as Crohn's disease, Behçet's disease and systemic lupus erythematosus. The sponsor indicated that PDR and of iCRVO are two different diseases and only iCRVO was further considered by the sponsor. The sponsor discussed CRVO, iCRVO and the targeted patient population where the product is intended to be used to prevent NVG. The COMP was of the opinion that the sponsor had not addressed the issues raised and did not accept the proposed approach due to difficulties in identifying an acceptable distinct medical entity.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 10 December 2013, prior to final opinion.

2.1.5 (2R,3R,4S,5R)-2-(6-amino-9H-purin-9-yl)-5-((((1r,3S)-3-(2-(5-(tert-butyl)-1Hbenzo[d]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl) amino)methyl)tetrahydrofuran-3,4-diol for treatment of acute myeloid leukaemia, Voisin Consulting S.A.R.L. - EMA/OD/141/13

[Co-ordinator: B. 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 significant benefit issue. The sponsor was requested to further discuss and to justify with any available data the proposed grounds of significant benefit.

In the written response and during an oral explanation before the Committee on 10 December 2013, the sponsor further discussed the results available up to date from the phase I clinical trial on haematologic malignancies, and the mechanism of action of the product, particularly in relation to the selectivity for the MLL rearranged leukaemic cells.

MLL-rearrangement in leukaemias can be the result of reciprocal chromosomal translocations involving 11q23, or from partial tandem duplication of MLL gene. The first is characteristic of both AML and ALL while the latter is mainly relevant to AML. The sponsor is selectively targeting MLL rearranged leukaemias based on the mechanism of action of the product and the selectivity in vitro on MLL rearranged leukaemic cells, although in first instance also patients without MLL-rearranged forms of AML and ALL were included in the Phase I trial. Even though the selectivity of the product appears

clear from the pre-clinical studies, suggesting the potential of treating more effectively the sub-population with MLL-rearranged leukaemias, the COMP was of the opinion that due to the early stage of development the data available up to date are not sufficient to support a possible claim of selectivity of the product for this sub-group of patients. Such selectivity is likely to be further confirmed in the on-going and future clinical studies, as suggested by the good clinical response of patients with MLL-rearranged AML in the phase I study (7 out of 13 AML patients enrolled).

The Phase I study on haematologic malignancies including AML (13 patients) and ALL (2 patients) was conducted on patients that had previous treatment cycles with different antineoplastic products to which they were refractory, or after which they relapsed. In these patients the product showed good clinical responses. Haematologic responses were favourable in both ALL and AML patients, with one ALL case resulting in 90% reduction of circulating blasts and blood and/or marrow maturation in 4 patients with AML. The responses were poorer in patients with non-MLL rearranged leukaemic forms.

The COMP considered that the applied product may be of significant benefit to those affected by the condition. The sponsor presented preliminary clinical data showing clinical response in patients affected by acute lymphoblastic leukaemia relapsed after previous treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by acute lymphoblastic leukaemia.

The Committee agreed that the condition, 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 (2*R*,3*R*,4*S*,5*R*)-2-(6-amino-9*H*-purin-9-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl) amino)methyl)tetrahydrofuran-3,4-diol was considered justified based on preclinical data and early clinical data showing antitumor activity of the proposed product. 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 less than 1 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (2*R*,3*R*,4*S*,5*R*)-2-(6-amino-9*H*-purin-9-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl) amino)methyl)tetrahydrofuran-3,4-diol may be of significant benefit to those affected by the condition. The sponsor presented preliminary clinical data showing clinical response in patients affected by acute lymphoblastic leukaemia relapsed after previous treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by acute lymphoblastic leukaemia.

A positive opinion for (2*R*,3*R*,4*S*,5*R*)-2-(6-amino-9*H*-purin-9-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl) amino)methyl)tetrahydrofuran-3,4-diol, for treatment of acute lymphoblastic leukaemia, was adopted by consensus.

2.1.6 (2R,3R,4S,5R)-2-(6-amino-9H-purin-9-yl)-5-((((1r,3S)-3-(2-(5-(tert-butyl)-1Hbenzo[d]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl) amino)methyl)tetrahydrofuran-3,4-diol

for treatment of acute lymphoblastic leukaemia, Voisin Consulting S.A.R.L. - EMA/OD/143/13
[Co-ordinator: B. 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 significant benefit issue. The sponsor was requested to further discuss and to justify with any available data the proposed grounds of significant benefit.

In the written response and during an oral explanation before the Committee on 10 December 2013, the sponsor further discussed the results available up to date from the phase I clinical trial on haematologic malignancies, and the mechanism of action of the product, particularly in relation to the selectivity for the MLL rearranged leukaemic cells.

MLL-rearrangement in leukaemias can be the result of reciprocal chromosomal translocations involving 11q23, or from partial tandem duplication of MLL gene. The first is characteristic of both AML and ALL while the latter is mainly relevant to AML. The sponsor is selectively targeting MLL rearranged leukaemias based on the mechanism of action of the product and the selectivity in vitro on MLL rearranged leukaemic cells, although in first instance also patients without MLL-rearranged forms of AML and ALL were included in the Phase I trial. Even though the selectivity of the product appears clear from the pre-clinical studies, suggesting the potential of treating more effectively the sub-population with MLL-rearranged leukaemias, the COMP was of the opinion that due to the early stage of development the data available up to date are not sufficient to support a possible claim of selectivity of the product for this sub-group of patients. Such selectivity is likely to be further confirmed in the on-going and future clinical studies, as suggested by the good clinical response of patients with MLL-rearranged AML in the phase I study (7 out of 13 AML patients enrolled).

The Phase I study on haematologic malignancies including AML (13 patients) and ALL (2 patients) was conducted on patients that had previous treatment cycles with different antineoplastic products to which they were refractory, or after which they relapsed. In these patients the product showed good clinical responses. Haematologic responses were favourable in both ALL and AML patients, with one ALL case resulting in 90% reduction of circulating blasts and blood and/or marrow maturation in 4 patients with AML. The responses were poorer in patients with non-MLL rearranged leukaemic forms.

The COMP considered that the applied product may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing clinical response in patients with acute myeloid leukaemia relapsed after previous treatments. The Committee considered that this constitutes a clinically relevant advantage for the patient population affected by the condition.

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

The intention to treat the condition with the medicinal product containing (2*R*,3*R*,4*S*,5*R*)-2-(6-amino-9*H*-purin-9-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl) amino)methyl)tetrahydrofuran-3,4-diol was considered justified based on preclinical and early clinical data showing antitumor activity of the product. The condition is life threatening 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 was estimated to be affecting approximately 1 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (2*R*,3*R*,4*S*,5*R*)-2-(6-amino-9*H*-purin-9-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl) amino)methyl)tetrahydrofuran-3,4-diol may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data

showing clinical response in patients with acute myeloid leukaemia relapsed after previous treatments. The Committee considered that this constitutes a clinically relevant advantage for the patient population affected by the condition.

A positive opinion for (2*R*,3*R*,4*S*,5*R*)-2-(6-amino-9*H*-purin-9-yl)-5-((((1*r*,3*S*)-3-(2-(5-(*tert*-butyl)-1*H*-benzo[*d*]imidazol-2-yl)ethyl)cyclobutyl)(isopropyl) amino)methyl)tetrahydrofuran-3,4-diol, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.1.7 Product for treatment of acute myeloid leukaemia - EMA/OD/147/13
[Co-ordinator: B. Dembowska-Bagińska]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation on 25 November 2013, prior to responding to the list of issues.

2.1.8 Product for treatment of Type 1 diabetes mellitus patients with residual beta-cell function - EMA/OD/128/13
[Co-ordinator: V. Tillmann]

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:

- Orphan indication

According to the legal basis of orphan designation and in particular guideline ENTR/6283/00 Rev03, a subset of a disease which, when considered as a whole, has a prevalence greater than 5 in 10 000, could be considered a valid condition if patients in that subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition and if such characteristics are essential for the medicinal product to carry out its action.

In addition, the guideline states that “different degrees of severity or stages of a disease would generally not be considered as distinct conditions”. The same applies to “subsets of patients in whom the medicinal product is expected to show a favourable benefit/risk”.

It is the opinion of the COMP that the proposed indication “type 1 diabetes mellitus patients with residual beta-cell function” is a stage rather than a subset of type I diabetes mellitus.

Type 1 diabetes mellitus patients with residual beta-cell function should therefore be justified as a distinct medical entity or a valid subset.

- Prevalence

In order to justify the prevalence of the proposed subset the sponsor should better elaborate on:

- the choice of the sources selected for the estimation of the prevalence of the condition, and in particular those leading to the proposed prevalence of 5.9 in 10,000 for type I diabetes as a whole. It is important to note that the COMP requires complete prevalence for designation, rather than 5-year prevalence

- the methodology used for the prevalence calculation, particularly regarding:

a) the extrapolations used to reach the proposed prevalence estimate of the patient population with residual B-cell function;

b) the case definition of residual beta cell function at single patient level and across different health care practices.

The sponsor was also invited to perform a sensitivity analysis of the proposed prevalence.

In the written response, and during an oral explanation before the Committee on 10 December 2013, the sponsor further elaborated its view on the proposed indication and the prevalence. However, the COMP maintained the view that the proposed indication is a stage of diabetes mellitus type I and not acceptable for designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 December 2013, prior to final opinion.

2.1.9 Product for treatment of Type 1 Diabetes Mellitus patients with residual beta-cell function - EMA/OD/075/13
[Co-ordinator: V. Tillmann]

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:

- Orphan indication

According to the legal basis of orphan designation and in particular guideline ENTR/6283/00 Rev03, a subset of a disease which, when considered as a whole, has a prevalence greater than 5 in 10 000, could be considered a valid condition if patients in that subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition and if such characteristics are essential for the medicinal product to carry out its action.

In addition, the guideline states that “different degrees of severity or stages of a disease would generally not be considered as distinct conditions”. The same applies to “subsets of patients in whom the medicinal product is expected to show a favourable benefit/risk”.

It is the opinion of the COMP that the proposed indication “type 1 diabetes mellitus patients with residual beta-cell function” is a stage rather than a subset of type I diabetes mellitus. Type 1 diabetes mellitus patients with residual beta-cell function should therefore be justified as a distinct medical entity or a valid subset.

- Medical plausibility

To establish if there exists a scientific rationale for the development of the proposed product for treatment of type 1 diabetes mellitus patients with residual beta-cell function the sponsor should further elaborate on the extrapolation of the immunologic responses showed in the 2010 study to the potential clinical efficacy of the product in the proposed patient population.

- Prevalence

In order to justify the prevalence of the proposed subset the sponsor should better elaborate on:

- the choice of the sources for the estimation of the prevalence of the condition, and in particular those sources leading to the proposed prevalence of 5.9 in 10,000 for type I diabetes as a whole. It is important to note that the COMP requires complete prevalence for designation, rather than 5-year prevalence

- the methodology used for the prevalence calculation, particularly regarding:

a) the extrapolations used to reach the proposed prevalence estimate of the patient population with residual B-cell function

b) the case definition of residual beta cell function at single patient level and across different health care practices

The sponsor was invited to provide a sensitivity analysis of the proposed prevalence.

- Justification of significant benefit

Assumptions of potential benefit(s) should be plausible and where possible based on sound pharmacological principles. It is to be noted that preclinical data and/or preliminary clinical information are usually required as supportive evidence.

The sponsor is therefore invited to discuss any available data to support the significant benefit of the proposed product.

In the written response, and during an oral explanation before the Committee on 10 December 2013, the sponsor further elaborated its view on the proposed indication and the prevalence. However, the COMP maintained the view that the proposed indication is a stage of diabetes mellitus type I and not acceptable for designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 December 2013, prior to final opinion.

2.1.10 Autologous dendritic cells pulsed with allogeneic tumour cell lysate for treatment of malignant mesothelioma, Amphera BV - EMA/OD/138/13
[Co-ordinator: A. Magrelli]

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

- Medical plausibility

The proposed product is autologous dendritic cells pulsed with allogeneic tumour cell lysate. The sponsor has submitted data with autologous dendritic cells pulsed with autologous tumour cell lysate in non-clinical in vivo models and a clinical study. One non-clinical in vivo study measured the effect autologous dendritic cells pulsed with allogeneic tumour cell lysate where only one of the 5 tumour cell lines was used has an effect in malignant mesothelioma. The sponsor should clarify the nature of their product as it appears as different to the products used in the submitted data and the relevance of the submitted data to their product.

- Justification of significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. Specific reference should be made regarding the relevance of their product which uses allogeneic tumour lysates versus the product in the clinical study which uses autologous tumour lysate.

In the written response, and during an oral explanation before the Committee on 11 December 2013, the sponsor presented data which supports the basis for bridging between dendritic cells pulsed with autologous tumour antigens and dendritic cells pulsed with allogeneic tumour antigens. This was based on animal studies which the sponsor has conducted. This data convincingly showed the overlap in the response in two different mouse strains thereby supporting the principle of bridging of data from autologous tumour antigen material and allogeneic tumour material. The sponsor then elaborated the problems of generating data in humans as each product is patient specific. The sponsor informed the COMP that they had produced samples of the product but that they had not tested it in patients as each time they needed to produce a batch which was patient specific. The COMP accepted the non-clinical in vivo data as the basis to support both the medical plausibility and the significant benefit. Regarding the significant benefit the alternative mode of action was considered as the basis to justify the principle and the non-clinical efficacy data in the two mouse strains as sufficient at this time to support the place of the alternative mode of action in this condition. The COMP concluded that the sponsor provided support for the alternative mode of action based on pre-clinical in vivo data, which could be extrapolated to improved overall survival in patients. The Committee considered that this could translate into a clinically relevant advantage.

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

The intention to treat the condition with the medicinal product containing autologous dendritic cells pulsed with allogeneic tumour cell lysate was considered justified based on data from preclinical in vivo models. The condition is life-threatening due to a very high mortality rate of mesothelioma where median survival is 9 months.

The condition was estimated to be affecting approximately 0.3 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous dendritic cells pulsed with allogeneic tumour cell lysate may be of significant benefit to those affected by the condition. The sponsor provided support for the alternative mode of action based on pre-clinical in vivo data, which could be extrapolated to improved overall survival in patients. The Committee considered that this could translate into a clinically relevant advantage.

A positive opinion for autologous dendritic cells pulsed with allogeneic tumour cell lysate, for treatment of malignant mesothelioma, was adopted by consensus.

2.1.11 **Allantoin** for treatment of epidermolysis bullosa, ORS Oxford Ltd - EMA/OD/145/13

[Co-ordinator: F. 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:

- Medical plausibility

The sponsor has presented literature data on the effects of the product on wound healing in general as well as clinical experience with the product. However, there are no data that address the mechanism of action of the product at molecular or cellular level in epidermolysis bullosa (EB).

To establish correctly if there exists a scientific rationale for the development of Allantoin for treatment of epidermolysis bullosa, the sponsor is asked to clarify why preclinical studies such as *in vitro* wound healing assays with cultured cells lacking collagen VII or one chain of laminin-332, or animal experiments using EB animal models have not been used to analyse the effects of allantoin in EB.

Further, the sponsor should discuss the currently used topical treatments including products containing allantoin in lower concentrations compared to the proposed product.

In the written response, and during an oral explanation before the Committee on 11 December 2013, the sponsor was of the view that preliminary clinical data from EB are superior data compared to data from animal or in vitro models. The sponsor also stated that allantoin in other products is unstable (data not shown) and attributes loss of efficacy over time with his own initial product, which had been used in the compassionate use programme, to the degradation of allantoin in the initial formulation. Allantoin in the new formulation is reportedly stable.

The sponsor also highlighted the ability of the new formulation with higher concentrations of allantoin to penetrate across various skin barriers according to experimental models using human or animal skin (% of allantoin crossing barrier, no further analysis).

The sponsor has presented literature data on the effects of the product on wound healing in general as well as clinical experience in an uncontrolled setting with the product. The literature data are quite old and may not have been performed according to current standards. Allantoin is contained as excipient in many cosmetic products, albeit at a lower concentration (usually 0.5%). A new formulation containing up to 9% of allantoin is proposed for the treatment of EB. Skin care is an integral part of symptomatic treatment for EB. Preserving skin moisture may reduce shearing due to mechanical stress and helps to reduce itching. Optimal moisture balance also contributes to healing of wounds.

The COMP discussed whether the results from other wounds can be extrapolated to EB and whether the clinical data presented without a clear pharmacological target for allantoin in EB can be accepted. With regard to the preclinical studies, the sponsor replied that these are difficult to perform as there is no animal model and biopsies are not possible. In vivo models in horses and dogs are under development but not available yet. The COMP was of the view that the extrapolation with not exactly the same product from the literature and describing general wound healing was of limited value into the applied condition.

With regard to the clinical studies, EB is reported to “cycle”, i.e. a loss of efficacy of skin care products after longer use. The initial response of the patients in the uncontrolled setting may therefore simply be due to the change of product. The COMP also discussed that the mechanism of action of the product is not linked to the genetic causes of EB. Despite this and the fact that there were concerns about the reliability of the clinical data, it was acknowledged that the sponsor has a product and there are clinical observations that support the action of the product in EB. This was considered sufficient at this stage to support the medical plausibility.

Taken together, the COMP considered that the intention to treat the condition with the medicinal product containing Allantoin was considered justified based on preliminary clinical observations seen in patients with epidermolysis bullosa. A recommendation for protocol assistance was expressed by the COMP for further discussion on the development

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

The intention to treat the condition with the medicinal product containing allantoin was considered justified based on preliminary clinical observations seen in patients with epidermolysis bullosa. The

condition is chronically debilitating and life-threatening, in particular due to severe generalised blistering resulting in poor quality of life and shortened life expectancy.

The condition was estimated to be affecting less than 0.8 in 10,000 people 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 allantoin, for treatment of epidermolysis bullosa, was adopted by consensus.

2.1.12 Product for treatment of ameloblastoma - EMA/OD/110/13
[Co-ordinator: B. Bloechl-Daum]

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

It is understood that the product is intended for reconstruction of bone defects of the craniomaxillofacial skeleton, due to surgical treatment of tumours of the corresponding region.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of ameloblastoma, the sponsor should further elaborate on the relevance for the treatment of ameloblastoma, and if considered appropriate amend the proposed indication.

In the written response, and during an oral explanation before the Committee on 11 December 2013, the sponsor acknowledged that the product does not treat “directly the condition” and discussed that they intended to treat a variety of conditions where bone deficits may be generated. However, they stressed that the treatment of ameloblastoma is always primarily surgical, and therefore they positioned their product in the treatment of the condition as proposed in this designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 December 2013, prior to final opinion.

2.1.13 Inecalcitol for treatment of Chronic Lymphocytic Leukaemia/ small lymphocytic lymphoma, Hybrigenics SA - EMA/OD/109/13
[Co-ordinator: B. 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 significant benefit issue.

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preliminary study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. This should be discussed within the context of the current European Guidelines.

In the written response, and during an oral explanation before the Committee on 11 December 2013, the sponsor presented the rationale for early treatment of patients with chronic lymphocytic leukaemia. According to the ESMO Guidelines (Annals of Oncology 22 (Supplement 6): vi50–vi54, 2011) there is currently no therapy for the target patient population the sponsor is targeting which is treatment of early, stable disease (Binet stage A and B without active disease; Rai 0, I and II without active disease). According to the ESMO *Guidelines Previous studies have shown that early treatment*

withalkylating agents does not translate into a survival advantage in patients with early stage CLL. The standard treatment of patients with early disease is a watch and wait strategy. Blood cell counts and clinical examinations should be performed every 3–12 months. The preliminary data produced by the sponsor would indicate that their product could be used in this patient population thereby delaying the time to progression to active disease. The COMP considered that at this stage the proposed alternative mode of action and the preliminary data produced by the sponsor were sufficient to support the assumption on significant benefit. The sponsor is strongly encouraged to come to Protocol Assistance for further discussion on the development and to discuss the requirement of significant benefit at the time of marketing authorisation.

The Committee agreed that the condition, 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 inecalcitol was considered justified based on preliminary clinical data in patients with the condition.

The condition is life-threatening due to an overall survival rate at 5 years of 65% following diagnosis. The condition was estimated to be affecting approximately 3.5 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing inecalcitol may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that the product could delay the progression of disease in high risk patients. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for inecalcitol, for treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma, was adopted by consensus.

2.1.14 Lonafarnib for the treatment of hepatitis delta virus (HDV) infection, Eiger Biopharmaceuticals Europe Limited - EMA/OD/132/13
[Co-ordinator: A. Corrêa Nunes]

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:

- Medical plausibility

The proposed condition should 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).

The sponsor is requested in particular to further elaborate on the paragraph of the above mentioned guideline according to which “Generally the intersection of two (or more) concomitant conditions would not be considered as a valid condition. However, it could be acceptable, if such intersection resulted in a certain new evaluable characteristic essential for the pharmacological effect and the medical outcome”.

- Prevalence

As it seems that the sponsor may have excluded part of the population affected by the condition by using an indirect calculation method based on the population at risk. The sponsor is invited to further

elaborate on the use of data in table 1 of the application to draw a conclusion on the prevalence of the proposed 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, and during an oral explanation before the Committee on 11 December 2013, the sponsor defended the validity of the proposed indication on the grounds that farnesylation is only relevant for HDV and not HBV viral cycle, and describes preliminary clinical data where inhibition of farnesylation does not affect the viral levels of HBV. It can be thus accepted that the proposed condition fulfils the provisioned guidance of the ENTR6283/00. Therefore the indication “treatment of Hepatitis delta virus infection” may be considered valid for the purpose of designation.

With regards to the prevalence issue, the sponsor rejected the request of the COMP to derive a more direct estimate based on the country data of table 1, on the basis that the studies that yield the percentage of HDV in HBV carriers are over inflated “up to several fold” because these prevalence values are taken from tertiary centers where referral bias is present. The sponsor mentions personal communications with key opinion learers, to support this view.

The sponsor focused on the second method of indirect calculation for prevalence based in high-risk groups, and varies some assumptions as in table 8, reaching a “worst case scenario of 4.11/10,000”.

The COMP accepted the presence of reference bias in tertiary centres with regards to the direct available data, and the methodology of the sponsor for the purpose of calculating the prevalence estimate. The COMP concluded to a “not more than 4” people in 10,000 for the purpose of prevalence calculation, but also noted that the time of marketing authorisation the prevalence criterion would have to be re-examined together with all other criteria.

The Committee agreed that the condition, hepatitis delta virus infection, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing lonafarnib was considered justified based on the preliminary clinical data conducted in patients with the condition.

The condition is life-threatening and chronically debilitating due to the development of cirrhosis, portal hypertension and liver insufficiency. The condition was estimated to be affecting not more than 4 in 10,000 people in the European Union, at the time the application was made; this was based on an extensive literature search conducted by the sponsor.

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 lonafarnib, for treatment of hepatitis delta virus infection, was adopted by consensus.

2.1.15 Product for treatment of progesterone receptor negative endometrial cancer in combination with progestin therapy - EMA/OD/097/13
[Co-ordinator: B. Bloechl-Daum][Expert: R. Elbers]

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

- Intention to treat

The COMP understands that the underlying condition, endometrial cancer, is not a rare condition in the EU. While the sponsor argues in that the subset follows the provisions of guideline ENTR/6283/00 this is not supported by data. In particular, the updated guideline on the format and content of the applications for orphan designation (ENTR/65283/00 Rev03) describes, inter alia, that a subset of a disease with a prevalence greater than 5 in 10,000 may be considered a valid condition if patients in that subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition and if such characteristics are essential for the medicinal product to carry out its action. With reference to the above mentioned requirements the sponsor is invited to elaborate based on data with regards to the following issues:

A. With reference to the "plausible link to the condition":

1. Further elaborate on the definition of PR positivity vis a vis the four versions appearing in the sponsor's application (LBA 10 or 50 fmol/mg, IHC 1 or 10% stained cells) and discuss the clinical characteristics of the proposed population that would differentiate them from other endometrial cancer patients.
2. Discuss whether PR status can be considered as a transient stage due to increasing genomic instability over the course of the disease; of note that different stages or degrees of severity of the condition may not be considered as valid conditions for designation.

B. With reference to the "exclusion of effects outside the subset" sponsor is also requested to further elaborate on the following issues:

a. the mechanism of action of the proposed product in the context of pathophysiology of endometrial cancer and the possible pharmacodynamic effects that may be exerted either as a monotherapy or as part of a combination treatment

b. to address the limitations of the preclinical models in terms of absence of controls.

c. to discuss the absence of clinically relevant endpoints in the preliminary clinical study cited.

- Prevalence

The sponsor should re-calculate the prevalence estimate given the substantial uncertainty about many of the assumptions regarding the prevalence, including examining other cut-off points for PR positivity.

- Justification of significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate versus all authorised products for the proposed condition.

In the written response, and during an oral explanation before the Committee on 11 December 2013, the sponsor gave the following answers to the issues raised by the COMP:

With regards to the medical plausibility

A1. The sponsor describes the different cut-oof points used in different studies and stresses that no guidelines for the recommended cut-oof point exist. No new data are provided.

A2. With regards to the PR status in relation to the genomic instability the sponsor does not answer, but instead says that it can be found in all stages of the condition. No new data are provided.

Ba. It is states that supraphysiologic cytotoxic conncentrations cannot be feasibly reproduced in the experimental settings. The basis of the question is not addressed and no new data are provided.

Bb. The absence of control is not addressed. The question did not relate to supraphysiologic concentrations. No new data are provided.

Bc. No new data / observations with other endpoint are provided in this question either.

With regards to the prevalence

The sponsor provides a short statement that in the early study using the 50fmol cut-off point the ratio of negative patients was 22.6%, and that the current estimate uses an up to 24% ratio. Therefore this response creates a paradox of the number of less than 10fm/mg to be higher than the number of less than 50fm/mg. Therefore this is not addressed either.

Significant benefit

The sponsor does not address the question by providing the requested comparison versus all authorised treatments. Instead, an argument of improved safety is put forward based on letters from Asian countries where the product is authorised.

In conclusion none of the questions are addressed and no new data are provided in the answer of the sponsor.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 December 2013, prior to final opinion.

2.1.16 Sodium nitrite for treatment of aneurysmal subarachnoid hemorrhage, Hope Pharmaceuticals, Ltd - EMA/OD/131/13
[Co-ordinator: M. Možina]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the significant benefit issue. The arguments on significant benefit are based on the new mechanism of action and the potential of using their product in combination with nimodipine to improve efficacy in the condition.

No data was submitted to support the basis of the significant benefit of using the product in combination. The sponsor should detail the results of any preclinical and clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 12 December 2013, the sponsor submitted some additional data from their Phase II study in patients with subarachnoid haemorrhage showing a dose ranging effect on clinical outcomes measures based on a recent Swiss publication when the product was given in combination with nimodipine. This was discussed within the context of the most current European Guidelines on the *Management of Intracranial Aneurysms and Subarachnoid Haemorrage (Cerebrovasc Dis 2013;35:93-112.* The clinical outcome measures reflected the place of therapy in the prevention of delayed ischemic deficit where the authorised treatment nimodipine 60mg/4hr is given orally. The COMP accepted the data that was presented by sponsor showing the clinically relevant advantage of using the product in combination as acceptable at this stage to grant designation as showing any change in this condition is difficult. The sponsor was strongly encouraged to go to protocol assistance to discuss the development and the requirement for significant benefit at the time of marketing authorisation.

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

The intention to treat the condition with the medicinal product containing sodium nitrite was considered justified based on pre-clinical in vivo and preliminary clinical data in patients with the condition.

The condition is life-threatening due to a high mortality rate which is at 5 years between 65-70%. The condition was estimated to be affecting approximately 1 in 10,000 people in the European Union, at the time the application was made;

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing sodium nitrite may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that support that when the applied product is administered in combination with nimodipine, the clinical outcome of the patients improved. The Committee considered that this constitutes a clinically relevant advantage.

Post-meeting note:

Due to lack of quorum, a positive opinion for sodium nitrite, for treatment of aneurysmal subarachnoid haemorrhage, was adopted by consensus via written procedure on 17 December 2013.

2.1.17 Obeticholic acid for treatment of Primary Sclerosing Cholangitis, Intercept Italia S.R.L. - EMA/OD/136/13
[Co-ordinator: L. Gramstad]

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

Since UDCA is authorised for the treatment of the condition in Europe, the sponsor was invited to discuss the significant benefit of the proposed product in relation to UDCA.

In the written response, and during an oral explanation before the Committee on 12 December 2013, the sponsor discussed the assumption on significant benefit over UDCA. In the view of the sponsor, despite the use of UDCA therapy as a treatment for PSC, the clinical benefit of the treatment is viewed as marginal and a substantial unmet medical need remains. In its discussion with the COMP, the sponsor further elaborated on the data that exist for use of UDCA in the condition.

The COMP finally agreed that the applied product may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate positive effects on liver fibrosis, cirrhosis, and a reduction of portal hypertension. The COMP considered that this could translate into a clinically relevant advantage for the patients. The sponsor is strongly advised to seek protocol assistance in order to further discuss the requirement for significant benefit at the time of marketing authorisation.

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

The intention to treat the condition with the medicinal product containing obeticholic acid was considered justified based on in vivo preclinical data where positive effects on liver fibrosis, cirrhosis, and a reduction of portal hypertension were seen.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure. The patients also have an increased risk of hepatobiliary cancer, including cholangiocarcinoma and gallbladder cancer as well as increased mortality. The condition was estimated to be affecting less than 1 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing obeticholic acid may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate positive effects on liver fibrosis, cirrhosis, and a reduction of portal hypertension.

A positive opinion for obeticholic acid, for treatment of primary sclerosing cholangitis, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1 (6aS)-1,10-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de, g]quinoline-2,9-diol

(6aS)-1,10-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de, g]quinoline-2,9-diol for treatment of dystrophic myotonia, Valentia BioPharma S.L - EMA/OD/133/13
[Co-ordinator: V. Stoyanova]

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

The intention to treat the condition with the medicinal product containing ((6aS)-1,10-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline-2,9-diol was considered justified based on preclinical in vivo studies using valid models of the condition which showed reduction of myotonia.

The condition is life-threatening and chronically debilitating due to dysfunction of several organs. In addition to chronic muscle weakness, the central nervous, cardiac, ocular and gastrointestinal systems can be affected to various degrees. Patients can have alterations of cardiac and ventilatory function, which can be fatal. Furthermore, mental disability, pain, and motor impairment are recognized features of myotonia type 1. The condition was estimated to be affecting less than 2 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing (6aS)-1,10-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo quinoline-2,9-diol may be of significant benefit to those affected by the condition. The product has an alternative mode of action and the sponsor has provided pre-clinical in vivo data in a valid animal model of the disease that support improved efficacy of the applied product compared to the authorised treatment. The Committee considered that this could translate into a clinically relevant advantage for the patients.

Post-meeting note:

Due to lack of quorum, a positive opinion for (6aS)-1,10-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline-2,9-diol, for treatment of dystrophic myotonia, was adopted by consensus via written procedure on 17 December 2013.

2.2.2 Product for treatment of cystic fibrosis - EMA/OD/156/13

[Co-ordinator: J. Eggenhofer]

The Committee considered that the following issues require clarification by the sponsor:

- Medical plausibility

The sponsor is invited to clarify the relevance of the animal model to the treatment of cystic fibrosis.

- Significant benefit

The sponsor is invited to further discuss the scientific basis of the proposed extrapolation of the beneficial clinical effects of azithromycin to the proposed product for treatment of patients affected by cystic fibrosis.

When such extrapolation is sufficiently justified, the sponsor is invited to further elaborate on the reasons for a potential clinically relevant advantage of azithromycin (and indirectly of the proposed product) in the framework of the currently authorised treatment regimen for cystic fibrosis.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the January meeting.

2.2.3 **Amatuximab** for treatment of malignant mesothelioma, Eisai Europe Limited - EMA/OD/108/13

[Co-ordinator: B. Dembowska-Bagińska]

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

The intention to treat the condition with the medicinal product containing amatuximab was considered justified based on preclinical data showing antitumor activity in mesothelioma cells and preliminary clinical data showing clinical response in patients affected by mesothelioma.

The condition is life-threatening due to the invasion of the pleura leading to pleural effusions, dyspnoea and malignant ascites. Local invasion may also result in obstruction of the superior vena cava, cardiac tamponade, and spinal cord compression. Patients with pleural mesothelioma usually die due to increasing tumour bulk that gradually fills the hemithorax causing progressive respiratory compromise ("incarceration" of the lungs), pneumonia, or myocardial dysfunction with arrhythmias. In patients with peritoneal mesothelioma, distension due to ascites, abdominal pain, and organ impairment such as bowel obstruction are observed. The condition was estimated to be affecting approximately 0.2 in 10,000 people in the European Union, at the time the application was made; the prevalence was estimated based on an analysis of the available literature, and on incidence data from international databases and the EU-funded Rarecare project on rare cancers.

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 amatuximab may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing favourable clinical response in patients treated with the proposed product in combination with standard of care treatment of malignant mesothelioma. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by malignant mesothelioma.

A positive opinion for amatuximab, for treatment of malignant mesothelioma, was adopted by consensus.

2.2.4 Product for treatment of cystic fibrosis - EMA/OD/159/13

[Co-ordinator: A. Lorence]

The Committee considered that the following issues require clarification by the sponsor:

- Number of people affected

The sponsor should describe and justify the methodology used for the prevalence calculation, taking into the consideration the duration of the condition, and to provide an updated calculation of time-point prevalence at the time the designation is made.

- Significant benefit

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

The sponsor is requested to further discuss the arguments provided based on data that would justify a clinically relevant advantage or major contribution to patient care

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the January meeting.

2.2.5 Product for treatment of epidermolysis bullosa - EMA/OD/149/13

[Co-ordinator: F. Naumann-Winter]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to diagnose, prevent or treat

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

  - the preliminary clinical data in particular the trial design and the interpretability of the results in the epidermolysis patients as the therapeutic impact of the proposed product in these patients does not appear to be clearly established.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the January meeting.

2.2.6 Product for prevention of delayed graft function after renal transplantation - EMA/OD/154/13

[Co-ordinator: K. Westermark]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to diagnose, prevent or treat

Ischemia reperfusion injury (IRI) is a cause of delayed graft function (DGF) in kidney transplantation. In addition, the pathogenetic mechanisms of IRI and DGF are also involved in organ rejection after transplantation. The sponsor presented preclinical data on ischemia reperfusion injury and early clinical

data in patients identified as having delayed graft function, within the development of the product for the prevention of antibody-mediated rejection after solid organ transplantation.

The sponsor is invited to clarify the main therapeutic target of the proposed product in this application, taking into account the mechanism of action of the product, and the current classification and case-definition of ischemia reperfusion injury and delayed graft function.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the January meeting.

2.2.7 Product for diagnosis of gastro-entero-pancreatic neuroendocrine tumours - EMA/OD/152/13
[Co-ordinator: K. Kubáčková]

The Committee considered that the following issues require clarification by the sponsor:

- Authorised treatments and significant benefit

It is the understanding of the COMP that in addition to Octreoscan, there is also another medicinal product that is authorised for the diagnosis of GEPNETs in Europe (^{99m}Tc-Tektrotyd in Poland). The sponsor should clarify which products are authorised for the diagnosis of the condition in Europe.

Based on the findings of this search over authorised products, the sponsor is asked to provide a discussion on the assumption of significant benefit of the applied product over all authorised diagnostic products, supported by any available data as far as possible.

The COMP adopted a list of issues that will be sent to the sponsor for a written response only.

2.2.8 Product for treatment of recent-onset Type 1 Diabetes with residual beta cell function - EMA/OD/157/13
[Co-ordinator: V. Tillmann]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to diagnose, prevent or treat

According to the legal basis of orphan designation and in particular guideline ENTR/6283/00 Rev03, a subset of a disease which, when considered as a whole, has a prevalence greater than 5 in 10 000, could be considered a valid condition if patients in that subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition and if such characteristics are essential for the medicinal product to carry out its action.

In addition, the guideline states that “different degrees of severity or stages of a disease would generally not be considered as distinct conditions”. The same applies to “subsets of patients in whom the medicinal product is expected to show a favourable benefit/risk”.

It is the opinion of the COMP that the proposed indication “type 1 diabetes mellitus patients with residual beta-cell function” is a stage rather than a subset of type I diabetes mellitus type 1 diabetes mellitus patients with residual beta-cell function should therefore be justified as a distinct medical entity or a valid subset.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of recent-onset type 1 diabetes with residual beta cell function, the sponsor should further elaborate on:

- the relevance of the preliminary clinical model used for the treatment of recent-onset type 1 diabetes with residual beta cell function, and the interpretation of the results obtained in the experiments,

- Number of people affected

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

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

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

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

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the January meeting.

2.2.9 Product for treatment of acute myeloid leukaemia - EMA/OD/150/13

[Co-ordinator: B. Dembowska-Bagińska]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to treat

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

- the results obtained in vitro on HL60 cell line
- the relevance of the in vitro data for the treatment of acute myeloid leukaemia, and the interpretation of the results obtained in the experiments,
- the absence of data in relevant in vivo preclinical models of AML or preliminary clinical settings in patients affected by the proposed condition

- Number of people affected

The sponsor should justify the duration of the disease, and clarify the methodology for drawing the final conclusion of 1 to 2 in 10,000.

- Significant benefit

The arguments on significant benefit are based on a new mechanism of action and the potential for improved efficacy in combination with de-methylating agents in patients not eligible for high intensity chemotherapy.

The sponsor is requested to elaborate on the results of the preclinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication and detail any clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the January meeting.

2.2.10 Product for treatment of perinatal asphyxia - EMA/OD/077/13
[Co-ordinator: K. Westermark]

The Committee considered that the following issues require clarification by the sponsor:

- Medicinal product applied for designation

It is stated in section E of the application that "the development of the formulation is still ongoing", and from the documents submitted so far by the sponsor it appears than no preclinical or clinical studies have been performed by the sponsor with any specific product containing the applied product.

The sponsor is invited to clarify:

a) if the specific product containing the proposed product as applied for designation is under development by the sponsor for the proposed indication.

b) the name of the manufacturer and the manufacturing site of such a product as per the updated guideline ENTR6283/00 Rev03,

c) the clinical rationale for developing an intravenous formulation,

d) the stage of development of the specific product, if such a product exists,

e) submit any available data pertaining to the product as applied for designation.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the January meeting.

2.2.11 Product for prevention of congenital cytomegalovirus infection following primary cytomegalovirus infection - EMA/OD/134/13
[Co-ordinator: N. Sypsas]

The Committee considered that the following issues require clarification by the sponsor:

- 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 congenital cytomegalovirus infection following primary cytomegalovirus infection due to the very early stage of development with the applied product in preventing maternal-foetal transmission of CMV in pregnant women who acquire primary CMV infection during pregnancy the sponsor should further elaborate on:

- the results obtained in vitro cell lines with their product in the prevention of congenital cytomegalovirus infection following primary cytomegalovirus infection;
- preliminary clinical safety data from both pre-clinical and clinical studies in healthy volunteer and renal transplant patients would indicate that the product may not be safe to use in pregnant women. The sponsor is further asked to elaborate on these safety findings in view of the fact that it is this target patient population to whom the treatment is intended to be administered. The sponsor is asked to further elaborate on the reported findings of the phase II study involving 20 recipients of renal transplant.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the January meeting.

2.2.12 N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino) phenyl)acrylamide benzenesulfonic acid salt for treatment of chronic lymphocytic leukemia / small lymphocytic lymphoma, Celgene Europe Limited - EMA/OD/151/13
[Co-ordinator: B. Dembowska-Bagińska]

The Committee agreed that the condition, 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 N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino) phenyl)acrylamide benzenesulfonic acid salt was considered justified based on preliminary clinical results in patients with relapsed or refractory disease that responded to treatment.

The condition is chronically debilitating and life-threatening due to development of 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 in a range of 3.8 to 4.7 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino) phenyl)acrylamide benzenesulfonic acid salt may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that patients who have relapsed or are refractory to the currently available products respond to treatment with the applied product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for N-(3-(5-fluoro-2-(4-(2-methoxyethoxy)phenylamino)pyrimidin-4-ylamino) phenyl)acrylamide benzenesulfonic acid salt, for treatment of chronic lymphocytic leukaemia / small lymphocytic lymphoma, was adopted by consensus.

2.2.13 Product for treatment for acute myeloid leukaemia - EMA/OD/160/13
[Co-ordinator: D. O'Connor]

The Committee considered that the following issues require clarification by the sponsor:

- Intention to treat

The constituents of the proposed product were not clear. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment for acute myeloid leukaemia, the sponsor should further elaborate on:

a) the particulars of the product in detail; the sponsor should specify any other plants that are used in its preparation, the form, solvents and excipients used, and provide as far as possible information for the herbal preparation according to the updated guideline EMA/HMPC/CHMP/CVMP/287539/2005 Rev.1

b) the details and relevance of the K562 model used for the treatment of the proposed condition as applied for designation

c) the clinical particulars and endpoints studied in the case study presented in section D3.

- Number of people affected

The sponsor should recalculate the prevalence taking into consideration the duration of the proposed condition.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy and safety in the proposed condition.

The sponsor is requested to provide evidence that supports the proposed claims on a novel mechanism based on data with the specific product subject of this application, provide a comparative discussion vis a vis the authorised products and discuss the expected position of the product in the management of AML patients in the context of current European guidelines for the treatment of the condition.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the January meeting.

2.3. Appeal procedure

2.3.1 5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine

5-Chloro-N2-[2-isopropoxy-5-methyl-4-(4-piperidinyl)phenyl]-N4-[2-(isopropylsulfonyl)phenyl]-2,4-pyrimidinediamine for treatment of non-small cell lung carcinoma (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive, Novartis Europharm Limited - EMA/OD/113/13
[Co-ordinator: B. Dembowska-Bagińska]

The COMP noted the negative opinion as adopted via written procedure on 18 November 2013. The sponsor's letter informing about the intent to submit the grounds for appeal for the 4-5 February 2014 COMP meeting was circulated for information.

2.4. Evaluation on-going

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

2.5. Validation on-going

The Committee was informed that validation was on-going for twenty seven one applications for orphan designation.

3. Requests for protocol assistance

3.1. Letters

The COMP was briefed on the significant benefit issues and adopted five protocol assistance letters for the following indications:

3.1.1 Product for treatment of malaria and for treatment of malaria in children

3.1.2 Product for treatment of Wilson's disease

3.1.3 Product for treatment of hepatocellular carcinoma

3.1.4 Product for treatment of acromegaly

3.1.5 Product for treatment of chronic non-infectious uveitis

3.2. 1st reports

The protocol assistance advice was discussed for final adoption in the forthcoming meetings for the following indications:

3.2.1 Product for treatment of ovarian cancer. The Committee also adopted the protocol assistance letter for this procedure.

3.3. On-going procedures

The Committee noted the following on-going protocol advice procedures:

3.3.1 Product for treatment of chronic lymphocytic leukaemia

3.3.2 Product for treatment of follicular lymphoma.

4. Overview of applications

4.1 Update on applications for orphan medicinal product designation submitted/expected

COMP co-ordinators were appointed for twenty six upcoming applications.

4.2 Update on orphan applications for Marketing Authorisation

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

5. Review of orphan designation for orphan medicinal products for Marketing Authorisation

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

5.1.1 Cholic Acid FGK for treatment of inborn errors of primary bile acid synthesis responsive to treatment with cholic acid; FGK Representative Service GmbH (EU/3/09/683) [Co-ordinator: A. Magrelli]

The COMP noted that the CHMP positive opinion was adopted at the November 2013 meeting.

The COMP concluded that:

- the proposed therapeutic indication "treatment of inborn errors of primary bile acid synthesis, responsive to treatment with cholic acid, in infants from one month of age for continuous lifelong treatment through adulthood, encompassing the following single enzyme defects: Sterol 27-hydroxylase (presenting as cerebrotendinous xanthomatosis, CTX) deficiency, 2- (or α-) methylacyl-CoA racemase (AMACR) deficiency,Cholesterol 7α-hydroxylase (CYP7A1) deficiency" 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 0.07 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.

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 Cholic Acid FGK (EU/3/09/683) from the EC Register of Orphan Medicinal Products was adopted by consensus.

5.1.2 Deltyba ((R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole) for treatment of tuberculosis; Otsuka Novel Products GmbH (EU/3/07/524) [Co-ordinator: V. Stoyanova]

The COMP noted the CHMP positive opinion adopted at the November 2013 meeting. The Committee considered that the significant benefit issue requires clarification by the sponsor.

On the basis of the assessment of the application, and according to the discussion held at the COMP meeting, the COMP requests the sponsor to answer the following list of issues.

The sponsor is invited to further elaborate on the significant benefit of the proposed product versus all products currently authorised in the EU for the treatment of MDR-TB and in the context of the current management of this condition. The discussion on significant benefit should be supported by any available data.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the January meeting.

5.1.3 Para-aminosalicylic acid Lucane (Para-aminosalicylic acid) for treatment of tuberculosis; Lucane Pharma SA (EU/3/10/826) [Co-ordinator: V. Stoyanova]

The COMP noted that the CHMP positive opinion was adopted at the November 2013 meeting. The Committee considered that the significant benefit issue requires clarification by the sponsor.

The sponsor is invited to further elaborate on the advantages of PAS-GR in the treatment of MDR-TB *vis a vis* the currently authorised treatments for this condition in Europe. The discussion on such advantages should be supported by any available data.

In relation to the significant benefit vs. the currently authorised formulation of para-aminosalicylic acid (PAS) the sponsor is invited to further elaborate on any available data supporting the existence of serious and documented difficulties with the current formulation and supporting the major contribution to patient care linked to the new proposed formulation.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the January meeting.

5.1.4 Masican N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole for treatment of malignant gastrointestinal stromal tumours; AB Science (EU/3/04/251)

The COMP noted the CHMP negative opinion adopted at the November 2013 meeting.

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

5.2.1 (3-[5-(2-fluoro-phenyl)-[1,2,4]oxadiazole-3-yl]-benzoic acid) for treatment of Duchenne muscular dystrophy; PTC Therapeutics Ltd (EU/3/05/278)

Discussion was postponed until update on progress of the MA procedure.

5.2.2 [Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt] for treatment of medullary thyroid carcinoma; TMC Pharma Services Ltd (EU/3/08/610)

Discussion was postponed until update on progress of the MA procedure.

5.2.3 Masitinib mesilate for treatment of pancreatic cancer; AB Science (EU/3/09/684)

Discussion was postponed until update on progress of the MA procedure.

5.2.4 Bedaquiline ((1R,2S) 6-bromo-alpha-[2-(dimethylamino)ethyl]-2-methoxy-alpha-(1-naphthyl)-beta-phenyl-3-quinolineethano) for treatment of tuberculosis; Janssen-Cilag International N.V. (EU/3/05/314)

The Committee held initial discussion.

5.2.5 Recombinant human N-acetylgalactosamine-6-sulfatase for treatment of mucopolysaccharidosis, type IVA (Morquio A syndrome); BioMarin Europe Ltd (EU/3/09/657)

5.2.6 (-)-17(cyclopropylmethyl)-1,14 ß-dihydroxy-4,5 alpha-epoxy-6ß-[N-methyl-trans-3-(3-furyl) acrylamido] morphinan hydrochloride for treatment of uremic pruritus; Toray International U.K. Limited (EU/3/02/115)

Discussion was postponed until update on progress of the MA procedure.

5.3. On-going procedures

5.3.1 Methyl 4,6-diamino-2-[1-(2-fluorobenzyl)-1H-pyrazolo[3,4-b]pyridine-3-yl]-5-pyrimidinyl(methyl)carbamate for treatment of pulmonary arterial hypertension including treatment of chronic thromboembolic pulmonary hypertension; Bayer Pharma AG (EU/3/07/518)

5.3.2 (1R,2R)-octanoic acid[2-(2',3'-dihydro-benzo[1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt for treatment of Gaucher disease; Genzyme Europe BV (EU/3/07/514)

5.3.3 Mifepristone for treatment of hypercortisolism (Cushing's syndrome) of endogenous origin; FGK Representative Service GmbH (EU/3/11/925)

5.3.4 Ramucirumab for treatment of gastric cancer; Eli Lilly Nederland B.V. (EU/3/12/1004)

5.3.5 N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-D-gamma-glutamyl-(2S)-2-amino-beta-alanyl-L-alpha-aspartyl-L-cysteine to be used with folic acid for diagnosis of positive folate receptor status in ovarian cancer; Endocyte Europe, B.V. (EU/3/12/1043)

5.3.6 Obinutuzumab for treatment of chronic lymphocytic leukaemia; Roche Registration Limited (EU/3/12/1054)

5.3.7 Ex vivo expanded autologous human corneal epithelium containing stem cells for treatment of corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns; Chiesi Farmaceutici S.p.A. (EU/3/08/579)

5.3.8 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H- pyrazolo [3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one for treatment of mantle cell lymphoma; Janssen-Cilag International N.V. (EU/3/13/1115)

5.3.9 Folic acid to be used with N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-D-gamma-glutamyl-(2S)-2-amino-beta-alanyl-L-alpha-aspartyl-L-cysteine for diagnosis of positive folate receptor status in ovarian cancer; Endocyte Europe, B.V. (EU/3/12/1044)

5.3.10 Dexamethasone (40 mg tablet) for treatment of multiple myeloma; Laboratoires CTRS (Cell Therapies Research & Services) (EU/3/10/745)

5.3.11 Sorafenib tosylate; Bayer HealthCare AG for:

- treatment of follicular thyroid cancer (EU/3/13/1199)
- treatment of papillary thyroid cancer (EU/3/13/1200)

5.3.12 Olaparib for treatment of ovarian cancer; AstraZeneca AB (EU/3/07/501)

5.3.13 [Nle4, D-Phe7]-alfa-melanocyte stimulating hormone, Afamelanotide for treatment of erythropoietic protoporphyria; Clinuvel (UK) Limited (EU/3/08/541)

5.3.14 Chimeric-anti-interleukin-6 monoclonal antibody for treatment of Castleman's disease; Janssen-Cilag International N.V.; (EU/3/07/508)

5.3.15 Tobramycin (inhalation use) for treatment of *Pseudomonas Aeruginosa* lung infection in cystic fibrosis; PARI Pharma GmbH (EU/3/09/613)

5.3.16 Vincaleukoblastin-23-oic acid, O4-deacetyl-2-[(2-mercaptoethoxy)carbonyl]hydrazide, disulfide with N-[4-[[(2-amino-3,4-dihydro-4-oxo-6-pteridinyl)methyl]amino]benzoyl]-L-gamma-glutamyl-L-alpha-aspartyl-L-arginyl-L-alpha-aspartyl-L-alpha-aspartyl-L-cysteine for treatment of ovarian cancer; Endocyte Europe, B.V. (EU/3/12/959)

6. Procedural aspects

6.1 Training session for patients and consumers involved in EMA activities held on 10 December 2013

The draft Agenda EMA/508479/2013 was circulated for information.

6.2 EMA Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) meeting with all eligible organisations held on 11 December 2013

The draft Agenda EMA/644851/2013 was circulated for information.

7. Any other business

7.1 Similarity group

The draft report on *Similarity in orphan medicines* (EMA/84728/2013) was circulated for comments in preparation for the discussion in the January meeting.

7.2 Public consultation on the *EC Guideline on the format and content of applications for designation as orphan medicinal products and on the transfer of designations from one sponsor to another* ENTR/6283/00 Rev 3.

The topic was postponed to the January meeting.

7.3 EMA/FDA/MHLW-PMDA Orphan Product Designation Workshop to be held on 10 March 2014 at the EMA

The Committee noted the dates for the Workshop.

List of participants

Chair:	
Bruno Sepodes	EMA representative
Vice-Chair:	
Lesley Greene	Volunteer patient representative for Eurordis
COMP Members:	
André Lhoir	België/Belgique/Belgien
Irena Bradinova	Бълга̀рия
Kateřina Kubáčková	Česká Republika
Frauke Naumann-Winter	Deutschland
Vallo Tillmann	Eesti
Nikolaos Sypsas	Ελλάδα
Josep Torrent Farnell	España
Annie Lorence	France
Adriana Andrić	Hrvatska
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italia
Ioannis Kkolos	Κύπρος
Aušra Matulevičienė	Lietuva
Henri Metz	Luxembourg
Judit Eggenhofer	Magyarország (present on first 2 days only)
Albert Vincenti	Malta
Violeta Stoyanova-Beninska	Nederland
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Österreich
Bożenna Dembowska-Bagińska	Polska
Ana Corrêa-Nunes	Portugal
Flavia Saleh	Romãnia
Martin Možina	Slovenija
Veijo Saano	Suomi/Finland
Kerstin Westermark	Sverige
Daniel O'Connor	United Kingdom
Birthe Byskov Holm	Volunteer patient representative for Eurordis
Pauline Evers	Patient representative representing the European Genetic Alliances Network
Aikaterini Moraiti	EMA representative
Observers:	
Maria Mavris	Eurordis
Experts:	
Rembert Elbers via TC	Bundesinstitut für Arzneimittel und Medizinprodukte, Germany (for 2.1.5)