EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Product Development Scientific Support

# Committee for Orphan Medicinal Products (COMP)

Minutes of the 8 - 10 October 2013 meeting

## Note on access to documents

Documents under points 1.1 and 2 to 7 cannot be released at present as they are currently in draft format or are classified as confidential. They will become public when adopted in their final form 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/548716/2013

The agenda was adopted. In addition a topic on adaptive licencing was proposed for discussion.

**1.2** Adoption of the minutes of the previous meeting, 3 - 4 September 2013 EMA/COMP/432621/2013

The minutes were adopted.

**1.3** Conflicts of Interest

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

The COMP secretariat was informed as follows:

- K. Kubackova (CZ) declared a potential conflict of interest for applications under agenda points 2.1.8, 2.1.9 and 2.2.18.

- EGAN received a grant from Novartis who has submitted dossiers to be considered for orphan designation at the current meeting. Nevertheless, no direct conflicts of interest have been identified for P. Evers, who represents EGAN in the COMP.

# 2. Applications for orphan medicinal product designation[1]

## 2.1. For opinion

**2.1.1** Product for treatment of neurotrophic keratitis - EMA/OD/184/12
*[Co-ordinators: K. Westermark / S. Tsigkos]*

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 for the development of the proposed product for treatment of neurotrophic keratitis, the sponsor was asked to further elaborate on the relevance of the preclinical model used for the treatment of neurotrophic keratitis, and the interpretation of the results obtained in the experiments.

- Prevalence

The sponsor was asked to re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition.

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

The sponsor was also invited to provide information regarding the numerous conditions that could cause the condition.

[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).

In the written response, and during an oral explanation before the Committee on 8 October 2013, the sponsor discussed the available preclinical models in the literature and explained why they may not be suitable in the context of this application. In particular, it was stated that a trigeminal coagulation model might not be suitable because of the distance of the lesion from the eye, and that models that use alcohol and capsaicin in the retro-orbital space are highly inflammatory. With regard to the prevalence issue, the sponsor further elaborated by reviewing the available epidemiological data for several underlying causes, and by performing a sensitivity analysis and recalculating the proposed estimate. The committee considered that full extent of the range of underlying causes of the condition and their impact on prevalence had not been adequately addressed. Taking also into consideration the multiplicity of the assumptions used, the committee considered that the sponsor did not establish that the prevalence criterion was met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 October 2013, prior to final opinion.

### **2.1.2** Product for treatment of acromegaly - EMA/OD/082/13

*[Co-ordinators: V. Tillmann / S. Aarum]*

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 for the development of proposed product for treatment of acromegaly, the sponsor should further elaborate on:

- the methodology used in the pre-clinical studies as well as the results from these studies and their relevance for the development of the product in acromegaly.

- to provide any other new data or information that may exist to support the efficacy of the product in the applied condition.

- Justification of significant benefit

With the limited data presented to support the efficacy of the product in acromegaly, the sponsor was requested to further discuss the arguments provided for significant benefit over existing authorised products, and to elaborate on the results to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 8 October 2013, the sponsor further elaborated on the available preclinical data obtained in vitro. The sponsor also discussed the profile of other products with the same mechanism of action. The committee considered that there were no new data submitted to address the questions posed and that the available data and justifications presented were not sufficient to answer the questions raised. Therefore the Committee considered that the sponsor had not established the intention to treat the condition and the significant benefit over existing satisfactory treatments.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 8 October 2013, prior to final opinion.

### 2.1.3 Autologous, ex vivo expanded CD4+-enriched leukocytes treated with the de-methylating agent 5-aza-2'-deoxycytidine for treatment of glioma, CytoVac A/S - EMA/OD/086/13

*[Co-ordinators: A. Magrelli / S. Tsigkos]*

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

- Proposed active substance

The sponsor was invited to further elaborate on the populations of leukocytes contained in the proposed product regarding their anti-tumour characteristics.

- Prevalence

The sponsor was invited to provide additional estimates based on 5-year prevalence, and given the uncertainty about the assumptions used in the calculation, to perform a sensitivity analysis in particular by varying the ratio of gliomas versus all intracranial tumours.

- Justification of significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the implicit argument of improved efficacy versus authorised products or other therapies (e.g. neurosurgical intervention) for the treatment of the condition.

In the written response, and during an oral explanation before the Committee on 8 October 2013, the sponsor confirmed that the product is a mixed population of autologous lymphocytes, primarily Cytotoxic T cells and Natural Killer cells. A table with FACS identified populations was also presented with the caveat that the optimum specifications are yet to be established. Taking this into consideration, the COMP considered renaming the product to "autologous ex-vivo-expanded leucocytes treated with 5-aza-2'-deoxycytidine".

As for the prevalence criterion, the sponsor recalculated and produced a new estimate, based on literature data from the RARECARE group.

Finally with regards to the significant benefit, the sponsor reiterated the available clinical data and reorientated the argumentation towards the significant benefit of improved efficacy.

For the purpose of orphan designation, the Committee for Orphan Medicinal Products (COMP) considered that autologous, ex vivo expanded CD4+-enriched leukocytes treated with the de-methylating agent 5-aza-2'-deoxycytidine should be renamed as "autologous ex-vivo-expanded leucocytes treated with 5-aza-2'-deoxycytidine".

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

The intention to treat the condition with the medicinal product containing autologous ex-vivo-expanded leucocytes treated with 5-aza-2'-deoxycytidine was considered justified based on preliminary clinical studies in relapsed glioma patients who responded to treatment.

The condition is chronically debilitating, in particular due to compression and invasion of the surrounding brain structures leading to neurological deficits, and life-threatening with poor overall survival. Survival for glioblastoma multiforme patients is less than 5% at 5 years post diagnosis. The condition was estimated to be affecting approximately 2.2 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 autologous ex-vivo-expanded leucocytes treated with 5-aza-2'-deoxycytidine may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing tumour responses in relapsed patients with glioma. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous ex-vivo-expanded leucocytes treated with 5-aza-2'-deoxycytidine, for treatment of glioma, was adopted by consensus.

**2.1.4 Defibrotide** for prevention of graft versus host disease, Gentium S.p.A. - EMA/OD/103/13
*[Co-ordinators: K. Westermark / S. Mariz]*

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 for the development of defibrotide for prevention of graft-versus-host disease, the sponsor should further elaborate on:

- the relevance of the methodology and results of the in vitro models used to show the effects in the prevention of graft-versus-host disease, in particular the relevance of the endothelial in vitro data with autologous HSCT.

- the relevance of the clinical data which appeared in the pivotal publication in the Lancet. As this publication reported on a study in veno-occlusive disease including rescue-treatment in the control group, the sponsor should give more detail regarding the post-hoc analysis accordly to GcHD. More information on the therapeutic approach used, including background treatment, extent of HLA mismatch (or other relevant risk factor for GvHD) was required.

- 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 was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from in vitro studies and the patient population as well as the standard of care used in the clinical post hoc analysis submitted to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 8 October 2013, the sponsor discussed the relevance of using endothelial cells in their in vitro models and further elaborated on the available clinical data from the paediatric study. With regards to the preliminary clinical data, it was stated that incidence of acute GvHD at day 30 and 100 was a secondary endpoint and results showed a reduction in GvHD grade II-IV in treated subjects. The COMP discussed the data with the sponsor and concluded that the data was sufficient to support the orphan medicinal designation at this stage but at the same time the sponsor was encouraged to seek Protocol Assistance for the design of the clinical studies needed to support the future development of the product.

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 defibrotide was considered justified based on pre-clinical in vivo data as well as clinical data showing improved survival of patients who have undergone bone marrow transplant.

The condition is life-threatening and chronically debilitating due to damage to the connective tissue and exocrine glands. Severe aGvHD (grade 3) has a poor prognosis with 25% long-term survival (5 years). The condition was estimated to be affecting 0.23 in 10,000 people in the European Union, at the time the application was made; the sponsor has based this calculation on a recent review article which did an extensive literature search.

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 defibrotide may be of significant benefit to the population at risk of developing the condition. The sponsor has provided preliminary clinical data which show that the preventative use of defibrotide reduced the incidence of acute graft-versus-host disease in patients undergoing bone marrow transplant. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for defibrotide, for prevention of graft-versus-host disease, was adopted by consensus.

### **2.1.5** Product for treatment of Adult Onset Still's disease - EMA/OD/099/13

*[Co-ordinators: A. Corrêa Nunes / S. Mariz]*

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. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of adult onset Still's disease, the sponsor should further elaborate on the relevance of the pre-clinical and clinical data submitted to support the effects of the product in the target condition as this data is derived from rheumatoid arthritis preclinical models, healthy volunteers and patients with rheumatoid arthritis and psoriasis.

In the written response, and during an oral explanation before the Committee on 9 October 2013, the sponsor explained the relevance of the collagen-induced arthritis mouse model used to support the application, and proposed that the data from this model can be extrapolated in the sought indication, on the basis of the common arthritis element in both conditions. The sponsor also attempted to bridge their clinical data in rheumatoid arthritis and psoriasis to adult onset Still's disease. The Committee considered that the differences and similarities of these conditions had not been analysed in detail and considered that the relevance of the bridging exercise was not clear and justified for the purpose of designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 9 October 2013, prior to final opinion.

### **2.1.6** Product for treatment of *Pseudomonas aeruginosa* infection in cystic fibrosis - EMA/OD/101/13

*[Co-ordinators: J. Eggenhofer / L. Fregonese]*

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

In order to establish the medical plausibility of treating the proposed condition with the proposed product, the sponsor was invited to further discuss:

- the extrapolation of the in vitro results on biofilms to the clinical manifestations of CF.

- the expected doses when translating in vitro results to the clinical setting

- Prevalence

The sponsor should provide as final estimate of the prevalence of the condition.

- Justification of significant benefit

The sponsor was invited to elaborate on the advantages of administering the two products in a fixed combination rather than separately, taking into account:

- the proposed mechanism of action at the base of the expected clinical effects of clarithromycin in cystic fibrosis;

- the position of tobramycin and clarithromycin in the current treatment algorithm of the disease;

- the possibility of increasing broad spectrum antibiotic resistances;

- the applicability of the inhalation route of a product containing clarithromycin, in particularly in relation to possible irritant effects on the airways.

In the written response, and during an oral explanation before the Committee on 9 October 2013, the sponsor further elaborated on the requested points, and in particular discussed the synergistic effects anticipated by the constituents of the product, discussing biofilm de-structuring, antibacterial, and anti-inflammatory aspects. The sponsor also further elaborated on the prevalence issue and presented available preclinical safety and toxicology data. The committee considered that the relevance of the models used would not allow for drawing clinically relevant conclusions with regards to the criteria for orphan designation.

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

### 2.1.7 Recombinant human insulin receptor monoclonal antibody-fused iduronate 2-sulfatase for treatment of mucopolysaccharidosis type II (Hunter's syndrome), Voisin Consulting S.A.R.L. - EMA/OD/091/13

*[Co-ordinators: V. Saano / S. Aarum]*

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 has concluded a prevalence of 0.08 in 10,000. It is not clear how this figure is established from the available data. Also, the sponsor has also calculated a considerably higher figure (1.45 in 10,000) when using incidence and duration of the disease.

The sponsor should explain how the final conclusion is drawn from the available data, and to clarify the discrepancy. If considered relevant, a re-calculation of the prevalence should be provided.

In the written response, the sponsor further elaborated on the issue raised. It was stressed that the epidemiological data are limited and since the introduction of the enzyme replacement therapy, the awareness of the disease may have affected the prevalence.

The sponsor summarised the existing data on prevalence and amended the proposed estimate to a range of 0.02-0.06 in 10,000. Taking into account the previous knowledge of the Committee and the fact that there is still variability in the figures provided, the Committee considered that the prevalence was not more than 1 in 10,000 at the time of the application.

The Committee agreed that the condition, mucopolysaccharidosis type II (Hunter's syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant human insulin receptor monoclonal antibody-fused iduronate 2-sulfatase was considered justified based on preclinical results showing that the product targets organs affected by the disease and that it reduces the accumulation of lysosomal substrate in skin fibroblasts cultured from patients affected with Hunter syndrome.

The condition is chronically debilitating due to neurological decline, cardiovascular and pulmonary complications and life-threatening as indicated by the survival of the patients that can be limited to 10-15 years. The condition was estimated to be affecting not more 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 recombinant human insulin receptor monoclonal antibody-fused iduronate 2-sulfatase may be of significant benefit to those affected by the condition. The sponsor has provided preclinical results supporting the assumption that the product may improve the neurological symptoms of the patients. The Committee considered that this could translate into a clinically relevant advantage.

A positive opinion for recombinant human insulin receptor monoclonal antibody-fused iduronate 2-sulfatase, for treatment of mucopolysaccharidosis type II (Hunter's syndrome), was adopted by consensus.

### 2.1.8 **Sorafenib tosylate** for treatment of follicular thyroid cancer, Bayer HealthCare AG (Leverkusen) - EMA/OD/092/13

*[Co-ordinators: K. Westermark / S. Aarum]*

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 has concluded a prevalence of 0.64 in 10,000 using a calculation with many percentages that may potentially insert uncertainties into the calculation. Also, the conclusion given by the sponsor is higher than that previously accepted by the Committee.

The sponsor should better explain 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.

In the written response, the sponsor has recalculated the estimate and provided a range with an upper and lower limit for the complete prevalence for the condition. The Committee concluded that the condition was estimated to be affecting 0.2-0.9 in 10,000 people in the European Union.

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

The intention to treat the condition with the medicinal product containing sorafenib tosylate was considered justified based on the results in locally advanced or metastatic radioactive iodine treatment-refractory differentiated thyroid cancer patients.

The condition is chronically debilitating due to the local symptoms such as hoarseness, difficulties in swallowing, neck and throat pain, and to symptoms due to the presence of metastasis. The condition can be life-threatening due to the progression of the tumour in case of no response to first-line treatment with surgery and $^{131}I$ treatment, and in case of development of metastasis with wide spread of the tumour. The condition was estimated to be affecting in the range of 0.2-0.9 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 sorafenib tosylate may be of significant benefit to those affected by the condition. The sponsor has provided clinical data form its phase 3 trial  data that demonstrate positive effects in locally advanced or metastatic RAI-refractory follicular thyroid cancer patients. This is a clinically relevant advantage as the current treatment options of locally advanced or metastatic RAI-refractory follicular thyroid cancer patients are limited.

A positive opinion for sorafenib tosylate, for treatment of follicular thyroid cancer, was adopted by consensus.

### 2.1.9 **Sorafenib tosylate** for treatment of papillary thyroid cancer, Bayer HealthCare AG (Leverkusen) - EMA/OD/093/13

*[Co-ordinators: K. Westermark / S. Aarum]*

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 has concluded a prevalence of 2.56 in 10,000 using a calculation with many percentages that may potentially insert uncertainties into the calculation. Also, the conclusion is higher than what is the current knowledge of the Committee.

The sponsor should better explain 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.

In the written response, the sponsor has recalculated the estimate and provided a range with an upper and lower limit for the complete prevalence for the condition. The Committee concluded that the condition was estimated to be affecting in the range of 1-3 in 10,000 people in the European Union.

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

The intention to treat the condition with the medicinal product containing sorafenib tosylate was considered justified based on the results in locally advanced or metastatic radioactive iodine treatment-refractory differentiated thyroid cancer patients.

The condition is chronically debilitating due to the local symptoms such as hoarseness, difficulties in swallowing, neck and throat pain, and to symptoms due to the presence of metastasis. The condition can be life-threatening due to the progression of the tumour in case of no response to first-line treatment with surgery and 131I treatment, and in case of development of metastasis with wide spread of the tumour. The condition was estimated to be affecting 1-3 patients 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 sorafenib tosylate may be of significant benefit to those affected by the condition. The sponsor has provided clinical data form its phase 3 trial data that demonstrate positive effects in locally advanced or metastatic RAI-refractory papillary thyroid cancer patients. This is a clinically relevant advantage as the current treatment options of locally advanced or metastatic RAI-refractory papillary thyroid cancer patients are limited.

A positive opinion for sorafenib tosylate, for treatment of papillary thyroid cancer, was adopted by consensus.

**2.1.10** Product for treatment of Fabry disease - EMA/OD/100/13
*[Co-ordinators: P. Evers / S. Aarum]*

As agreed during the previous meeting, a list of issues was sent to the sponsor for response.

The COMP was informed that the sponsor withdrew the application on 23 September 2013 prior to responding to the list of questions.

## 2.2. For discussion / preparation for an opinion

**2.2.1** Product for treatment of primary biliary cirrhosis - EMA/OD/121/13
*[Co-ordinators: A. Corrêa Nunes / L. Fregonese]*

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

- Prevalence

The sponsor is invited to explain the methodology that lead to the proposed prevalence figures from the retrieved literature sources.

- Justification of significant benefit

The sponsor is invited to discuss significant benefit versus any products authorised in the EU for the treatment of intra- and extra-hepatic cholestasis associated pruritus, in addition to the products specifically authorised for primary biliary cirrhosis including e.g. cholestyramine in addition to UDCA.

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

**2.2.2** Product for treatment of Alagille syndrome - EMA/OD/120/13
*[Co-ordinators: A. Corrêa Nunes / L. Fregonese]*

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

- Justification of significant benefit

The sponsor states that there are no products authorised for the treatment of the condition in the European Union. However products exist that are authorised in the EU for the treatment of intra- and extra-hepatic cholestasis associated pruritus. To the knowledge of the Committee this would include also Alagille syndrome, which is a cause of intrahepatic cholestasis. The sponsor is therefore invited to discuss significant benefit of the proposed product versus currently authorised products for treatment of cholestasis in the EU, including e.g. cholestyramine and UDCA.

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

**2.2.3** Product for treatment of primary familial intrahepatic cholestasis - EMA/OD/123/13
*[Co-ordinators: J. Torrent-Farnell / L. Fregonese]*

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

- Justification of significant benefit

The sponsor states that there are no products authorised for the treatment of the condition in the European Union. However products exist that are authorised in the EU for the treatment of intra- and extra-hepatic cholestasis associated pruritus. To the knowledge of the Committee this would include also primary familiar intrahepatic cholestasis, which is a cause of intrahepatic cholestasis. The sponsor is therefore invited to discuss significant benefit of the proposed product versus currently authorised products for treatment of cholestasis in the EU, including e.g. cholestyramine and UDCA.

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

**2.2.4** Product for treatment of primary sclerosing cholangitis - EMA/OD/127/13
*[Co-ordinators: A. Corrêa Nunes / L. Fregonese]*

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

- Prevalence

The sponsor is invited to explain the methodology that lead to the proposed prevalence figures from the retrieved literature sources.

- Justification of significant benefit

Since UDCA seems to be authorised for the treatment of the condition in Europe, the sponsor is invited to discuss the significant benefit.

In addition products are authorised in the EU for the treatment of intra- and extra-hepatic cholestasis associated pruritus. To the knowledge of the Committee this would include also primary sclerosing cholangitis, which is a cause of intrahepatic cholestasis. The sponsor is therefore invited to discuss significant benefit of the proposed product versus the currently authorised products for treatment of primary sclerosing cholangitis and more in general for the treatment of cholestasis in the EU.

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

**2.2.5** Product for treatment of non-small cell lung carcinoma (NSCLC) that is anaplastic lymphoma kinase (ALK)-positive - EMA/OD/113/13
*[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]*

The Committee is of the opinion that non-small cell lung cancer is not a rare condition, and that the sponsor is restricting the orphan indication in patients that are "anaplastic lymphoma kinase positive".

While the sponsor argues in its scientific application by defining the subset of ALK patients as a group with "distinct clinical, pathological and prognostic features" several aspects pertaining to the acceptability of this subset have not been addressed. 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 with regards to the following issues:

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

1. As it appears that the sponsor is focusing only on EML4/ALK fusion rearrangements for the calculation of prevalence estimates, it should be clarified whether the proposed indication also comprises other ALK rearrangements, such as for example fusions with 5' partners like KIF5B and TFG. The impact of including all possible rearrangements to the population should be clearly discussed.
2. In line with the above, the potential existence of any primary activating mutations of ALK that may render the kinase constitutively active without being fused to other 5' partners should also be discussed, and the effect in the population addressed.
3. The definition of ALK positive tumours and the setting of the cut-off point of 15% of positive cells by the FISH test. The sponsor should elaborate on the available diagnostics to detect ALK rearrangements and provide a justification why the product might not have pharmacodynamic effects in lower cut-off points.
4. Whether it is relevant to use ALK positivity for the purpose of definition of a subset of non-small cell lung cancer, given that these rearrangements can be found in many solid tumours and haematopoietic malignancies acting as oncogenes in the pathophysiology of cancer.
5. Whether ALK-positive status of a lung tumour 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.
6. The assertion that there may exist "some limitations" in the notion that "ALK-rearrangement defines a subset of NSCLC with distinct clinical, pathological and prognostic features"; the sponsor is invited to further elaborate on these limitations.

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

a) the role of other pathways inhibited by the product in the pathophysiology of non-small cell lung cancer and the possible pharmacodynamic effects of the product though inhibition of these pathways;

b) to provide the internal data, investigating the effects of the product in an additional preclinical tumour models and to clarify if anti-tumour activity has been identified in models without ALK rearrangements;

c) to support by data the note that inhibition of other pathways may not be achievable at reasonably tolerated dose and to discuss the possible pharmacodynamic effects of the product vis a vis the fact that benefit/risk considerations are not sufficient to define a distinct condition (ENTR/6283/00 Rev 03);

d) with reference to the preliminary clinical data discussed, to clarify the inclusion of patients not having a confirmed EML4-ALK rearrangement and discuss the effects observed specifically in these patients.

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

### **2.2.6** Product for treatment of fragile X syndrome - EMA/OD/114/13

*[Co-ordinators: V. Stoyanova / S. Mariz]*

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

- Medical plausibility

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

- the lack of non-clinical in vivo studies to support the proof of concept that the proposed product may work in the condition;

- the relevance of the studies which are open label and included patients who were heavily treated already with one or more psychotropic drugs. CGI was used as primary outcome measurement. Although no disease specific scales exist, other scales such as the Social Responsiveness Scale (SRS), and Attention Deficit Hyperactivity Disorder Rating Scale-IV (ADHDRS) would have been more appropriate.

- Prevalence

The sponsor is invited to perform a prevalence calculation. For further information the sponsor should refer to section 1.3 Methods for Combining Data Identified, in the guidance document "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

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

### **2.2.7** Product for treatment of glioma - EMA/OD/107/13

*[Co-ordinators: H. Metz / S. Mariz]*

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

- Medical plausibility

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

- the composition of the sponsor's product and how it is produced;

- the relevance of the clinical cases submitted by the sponsor in view of limited effect and the very advanced stage of glioma in the patients treated;

- the sponsor is further invited to discuss the efficacy data.

- 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 should elaborate in further detail the relevance of the clinical cases that were submitted in view of the advanced stage of the patients.

The sponsor should further elaborate on the potential risks with the product and how this compares with the safety profile of current authorised medicinal products for the same condition.

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

**2.2.8** Product for treatment of graft-versus-host disease - EMA/OD/126/13
*[Co-ordinators: K. Westermark / L. Fregonese]*

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

- Prevalence

The sponsor is invited to re-examine the prevalence calculations taking into account also chronic GvHD, since the Committee is of the opinion, supported by scientific data on the current classification, that chronic forms should be included under the broader condition of graft-versus-host disease.

- Justification of significant benefit

The sponsor is requested to further elaborate on any available data to support the significant benefit of the proposed product in the treatment of graft-versus-host disease.

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

**2.2.9 Human monoclonal antibody against human interleukin 13** for treatment of eosinophilic esophagitis, Novartis Europharm Limited - EMA/OD/118/13
*[Co-ordinators: A. Lhoir / L. Fregonese]*

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

The intention to treat the condition with the medicinal product containing human monoclonal antibody against human interleukin 13 was considered justified based on preclinical data and on preliminary clinical data showing reduction of eosinophil numbers in the oesophageal mucosa.

The condition is chronically debilitating due to chronic oesophageal inflammation, with development of dysphagia that affects dietary intake, and with oesophageal stenosis that can be treated only with invasive procedures. The increased fragility of the oesophageal wall due to the chronic inflammation can lead to oesophageal perforation, particularly during the endoscopic procedures needed for treating the stenosis. The condition was estimated to be affecting less than 5 in 10,000 people in the European

Union, at the time the application was made. The prevalence was estimated by the sponsor based on literature search.

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 human monoclonal antibody against human interleukin 13, for treatment of eosinophilic oesophagitis, was adopted by consensus.

**2.2.10** Product for treatment of follicular lymphoma - EMA/OD/111/13
*[Co-ordinators: B. Dembowska-Bagińska / S. Mariz]*

The Committee considered that the prevalence issue requires clarification by the sponsor. The sponsor is asked to recalculate the prevalence taking into account the clinical heterogeneity of the disease, its rising incidence and recent treatment approaches and to present appropriate sensitivity analyses with respect to the critical assumptions.

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

**2.2.11 Ibrutinib** for treatment of diffuse large B-cell Lymphoma, Janssen-Cilag International N.V. - EMA/OD/116/13
*[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]*

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

The intention to treat the condition with the medicinal product containing ibrutinib was considered justified based on relevant preclinical models showing inhibition of tumour growth and preliminary clinical data showing responses in patients affected by the condition.

The condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract and bone marrow and life-threatening with 5-year survival rates reported as low as approximately one in four patients for the high risk group. The condition was estimated to be affecting approximately 2.4 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 ibrutinib may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate responses in patients that were refractory or had relapsed following previous treatments. The Committee considered that this constitutes a clinically relevant advantage.

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

**2.2.12** Product for prevention of necrotizing enterocolitis - EMA/OD/112/13
*[Co-ordinators: S. Thorsteinsson / S. Tsigkos]*

The Committee considered that the prevalence issue requires clarification by the sponsor. 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 population at risk and in particular the exclusion of non-premature neonates and/or neonates without low birth weight from the calculation of the number of patients eligible for prevention.

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

**2.2.13** Product for treatment of hypoparathyroidism - EMA/OD/102/13
*[Co-ordinators: K. Westermark / S. Aarum]*

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

- Condition

The sponsor has discussed the aetiology of hypoparathyroidism with regards to the post-surgical and non-surgical hypoparathyroidism. However, the exact scope of the proposed indication is not clear from the provided information. The sponsor is asked to clarify all the non-surgical forms of hypoparathyroidism that are proposed to be included in the proposed indication, in addition to the post-surgical form of the disease.

- Prevalence

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 provide a more detailed prevalence calculation taken into account all different forms of hypoparathyroidism (both post-surgical, idiopathic and other non-surgical hypoparathyroidism) corresponding to the proposed indication.

The data to support the prevalence of the post-surgical hypoparathyroidism is based on data from only a few Member States and should be substantiated with all available data. 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.

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

**2.2.14 Sirolimus** for prevention of arteriovenous access dysfunction in patients undergoing surgical creation of an arteriovenous access for haemodialysis, S-Cubed Limited - EMA/OD/117/13
*[Co-ordinators: D. Krievins / S. Aarum]*

The Committee agreed that the condition, arteriovenous access dysfunction in patients undergoing surgical creation of an arteriovenous access for haemodialysis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sirolimus was considered justified based on preclinical results and early clinical experience. In the preclinical models, the product decreased the intimal hyperplasia and the formation of stenosis.

The condition is chronically debilitating and potentially life threatening as it may lead to inactive dialysis and subsequent deterioration of the renal function. The condition was estimated to be affecting in the range of 2.9-4.4 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 sirolimus, for prevention of arteriovenous access dysfunction in patients undergoing surgical creation of an arteriovenous access for haemodialysis, was adopted by consensus.

**2.2.15 Soraprazan** for treatment of Stargardt's disease, Katairo GmbH - EMA/OD/124/13
*[Co-ordinators: D. Krievins / S. Aarum]*

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

The intention to treat the condition with the medicinal product containing soraprazan was considered justified based on preclinical results showing that the product removed lipofuscin from retinal pigment epithelial cells in a valid model of the disease.

The condition is chronically debilitating, in particular due to loss of visual acuity and central vision loss, which may progress to complete blindness. The condition was estimated to be affecting approximately 1-1.3 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 soraprazan, for treatment of Stargardt's disease, was adopted by consensus.

**2.2.16 Synthetic 12 amino acids peptide designed after subcommissural organ-spondin** for treatment of spinal cord injury, Neuronax SAS - EMA/OD/119/13
*[Co-ordinators: M. Možina / S. Tsigkos]*

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

The intention to treat the condition with the medicinal product containing synthetic 12 amino acids peptide designed after subcommissural organ-spondin was considered justified based on testing on preclinical models that produced improved functional outcomes compared to non-treated subjects.

The condition is chronically debilitating due to sensory and motor loss of function in the limbs, and life-threatening due to overall reduced life expectancy. The condition was estimated to be affecting less than 4.2 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 synthetic 12 amino acids peptide designed after subcommissural organ-spondin may be of significant benefit to those affected by the condition. The sponsor has provided preclinical

data suggesting that the proposed product may promote survival, outgrowth, synaptogenesis and myelination of neuronal cells, as well as preclinical studies showing improved functional outcomes in the treated groups. The sponsor has thus described a novel mechanism of action that may translate into improved effects for patients affected by the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for synthetic 12 amino acids peptide designed after subcommissural organ-spondin, for treatment of spinal cord injury, was adopted by consensus.

**2.2.17 Tivantinib** for treatment of hepatocellular carcinoma, Daiichi Sankyo Development Ltd - EMA/OD/115/13
*[Co-ordinators: F. Naumann-Winter / S. Mariz]*

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

The intention to treat the condition with the medicinal product containing tivantinib was considered justified based on preliminary clinical data in patients with advanced hepatocellular carcinoma.

The condition is life-threatening because is often discovered when it is in advanced phase, and survival following diagnosis is approximately 6 to 20 months. The main chronically debilitating manifestations of the condition include abdominal pain, weight loss, ascites, encephalopathy, jaundice and variceal bleeding. The condition was estimated to be affecting approximately 1 in 10,000 people in the European Union, at the time the application was made; the sponsor has used EUCAN and GLOBOCAN databases to establish the prevalence.

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 tivantinib may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that tivantinib may be effective in prolonging the time to progression in patients with advanced hepatocellular carcinoma who are refractory to sorafenib. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for tivantinib, for treatment of hepatocellular carcinoma, was adopted by consensus.

**2.2.18 Trebananib** for treatment of ovarian cancer, Amgen Europe BV - EMA/OD/122/13
*[Co-ordinators: B. Bloechl-Daum / S. Tsigkos]*

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

The intention to treat the condition with the medicinal product containing trebananib was considered justified based on preclinical models showing inhibition of tumour growth in treated subjects and preliminary clinical data showing improvements in Progression Free survival in patients with recurrent disease as an add-on to paclitaxel.

The condition chronically debilitating in particular due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years. The condition was estimated to be affecting less than 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 trebananib may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients with recurrent ovarian cancer that demonstrate that combination of the product with paclitaxel results in improved Progression free survival compared to paclitaxel alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for trebananib, for treatment of ovarian cancer, was adopted by consensus.

### 2.3. Evaluation on-going

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

### 2.4. Validation on-going

The Committee was informed that validation was on-going for thirteen applications for orphan designation.

## 3. Requests for protocol assistance

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

**3.1** Treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukemic/disseminated)

**3.2** Treatment of chronic lymphocytic leukaemia

**3.3** Treatment of ovarian cancer

**3.4** Treatment of mercury toxicity

The pending from the September meeting protocol assistance letter for treatment of myelofibrosis was also discussed and adopted.

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

**3.5** Treatment of graft-versus-host disease

**3.6** Treatment of Fabry disease

**3.7** Treatment of Wilson's disease

**3.8** Treatment of hepatocellular carcinoma

**3.9** Treatment of malaria

**3.10** Treatment of chronic iron overload requiring chelation therapy.

## 4. Overview of applications

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

COMP co-ordinators were appointed for 1 application submitted and 27 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

There were no products for discussion under this heading.

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

**5.2.1 Opsumit** (Macitentan) for treatment of pulmonary arterial hypertension; Actelion Registration Ltd. (OD/023/11, EU/3/11/909, EMA/H/C/002697), [Co-ordinators: V. Saano / L. Fregonese]
CHMP opinion: 21-24 October 2013

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to elaborate on the significant benefit issue. The sponsor was invited to further discuss and support as much as possible with data the significant benefit of Opsumit in relation to currently authorised therapies, in particular endothelin receptor antagonists.

In its written response, and during an oral explanation before the Committee on 9 October 2013, the sponsor further elaborated on the significant benefit issue. The sponsor stressed that the product was a novel ERA with demonstrated benefit on clinically relevant outcomes (morbidity-mortality) of PAH-related irreversible disease progression. It was also stated that it demonstrated benefit on outcome events when used in monotherapy and combination with currently approved and commonly prescribed PAH medicines, as well as that the product showed an improved liver safety profile compared with bosentan and lower incidence of adverse events of fluid retention vs. ambrisentan. Based on these arguments, the sponsor asserted that this compares favourably with other approved ERAs. The COMP discussed the available data on indirect comparison specifically versus other ERAs, and invited the sponsor to submit further discussion of the available data and expand the written justifications of significant benefit in relation to the currently authorised ERAs

The final COMP position on the review of the orphan medicinal product designation for macitentan (opsumit) will be discussed following the outcome for the CHMP assessment of the application for marketing authorisation for Opsumit.

**5.2.2 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-ordinators: A. Magrelli / S. Tsigkos]

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

**5.2.3 Cometriq** [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) [Co-ordinators: B. Bloechl-Daum / S. Aarum]

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

**5.2.4 Masican** N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole for treatment of malignant gastrointestinal stromal tumours; AB Science (EU/3/04/251) [Co-ordinators: D. O'Connor / S. Mariz]

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

**5.2.5 PAS-GR** (Para-aminosalicylic acid) for treatment of tuberculosis; Lucane Pharma SA (EU/3/10/826) [Co-ordinators: V. Stoyanova / S. Mariz]

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

**5.2.6 Sirturo** [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) [Co-ordinators: N. Sypsas / L. Fregonese]

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

**5.2.7 Translarna** (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) [Co-ordinators: P. Evers / S. Aarum]

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

**5.2.8 Vantobra,** Tobramycin (inhalation use) for treatment of *Pseudomonas Aeruginosa* lung infection in cystic fibrosis; PARI Pharma GmbH (EU/3/09/613,) [Co-ordinators: J. Eggenhofer, V. Stoyanova / L. Fregonese]

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

## 5.3. On-going procedures

**5.3.1 Adempas** (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 Cyramza** (Ramucirumab) for treatment of gastric cancer; Eli Lilly Nederland B.V. (OD/030/12)

**5.3.3 Delamanid** ((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)

**5.3.4 Folcepri** (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)

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

**5.3.6 Holoclar** (former name: GPLSCD01) (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)

**5.3.7 Masiviera (formerly Kinaction)** (Masitinib mesilate) for treatment of pancreatic cancer; AB Science (EU/3/09/684)

**5.3.8 Neocepri** (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)

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

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

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

**5.3.12 Vynfinit** (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)

**5.3.13 Winfuran** (-)-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).

# 6. Procedural aspects

**6.1** Validation issues for submitted application for treatment of cognitive disease in MPS II patients

The COMP adopted a letter to be sent to the sponsor in response to the submitted application.

# 7. Any other business

**7.1** Reorganisation of the EMA

The Committee was briefed on the new structure on the EMA.

**7.2** First PDCO/COMP workshop on conditions in rare diseases on 9 October 2013

The draft Agenda EMA/586210/2013 was circulated.

The Committees met to discuss the determination of the condition in rare diseases vis a vis the orphan and paediatric regulatory frameworks. Members of both committees discussed the ways forward to address the public health needs optimally in both orphan diseases and children's health. Both Committees acknowledged importance of the problem and committed themselves to work together to overcome the potential negative impact of their mutual decisions. Creation of the inter-active working group was agreed, where members of both Committees would regularly meet to:

- minimise the risks of different ways of determination of conditions in PDCO and COMP opinions
- identify situations when scientific committees cannot avoid different views
- suggest ways to achieve the best serving to public health in both fields of rare diseases and children's health with respect to both legislations.

Creation of the inter-active PDCO/COMP working group is planned at next plenary meetings in November. Volunteers willing to contribute to the work of this working group were invited to express their interest to their Committee secretariat.

**7.3** The European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP)

The Committee members were informed about the call for expression of interest for appointment or re-appointment of the COMP representative to the ENCePP Steering Group for 2014-2016 term at the November 2013 COMP meeting.

**7.4** Proposal for a publication strategy (including book on rare diseases)

The topic was postponed.

**7.5** Results on the survey on orphan medicinal products development

The topic was postponed.

**7.6** Grounds of major contribution to patient care

The topic was postponed.

**7.7** Similarity group

The topic was postponed.

**7.8** Scientific Coordination Board

The topic was postponed.

**7.9** Informal COMP meeting under Lithuanian presidency

The topic was postponed.

**Additional topic:**

The COMP discussed the adaptive licencing issues.

# Date of next COMP meeting: 5 - 6 November 2013

# List of participants

**Chair:**

Bruno Sepodes

**Vice-Chair:**

| | |
|---|---|
| Lesley Greene | Volunteer patient representative for Eurordis |

**COMP Members:**

| | |
|---|---|
| André Lhoir | België/Belgique/Belgien |
| Irena Bradinova | Бълга̀рия |
| Kateřina Kubáčková | Česká Republika |
| Vacant | Danmark |
| Frauke Naumann-Winter | Deutschland |
| Vallo Tillmann | Eesti |
| Geraldine O'Dea | Éire/Ireland |
| Nikolaos Sypsas | Ελλάδα |
| Josep Torrent Farnell | España |
| Annie Lorence | France (present on 1st and 2nd day only) |
| Sigurdur B. Thorsteinsson | Iceland |
| Armando Magrelli | Italia |
| Ioannis Kkolos | Κύπρος |
| Dainis Krievins | Latvija |
| Judit Eggenhofer | Magyarország |
| Albert Vincenti | Malta |
| Violeta Stoyanova-Beninska | Nederland |
| Lars Gramstad | Norway |
| Brigitte Blöchl-Daum | Österreich (present on 1st and 2nd day only) |
| Bożenna Dembowska-Bagińska | Polska |
| Ana Corrêa-Nunes | Portugal |
| Flavia Saleh | Romãnia |
| Martin Možina | Slovenija |
| Nomination pending | Slovensko |
| Veijo Saano | Suomi/Finland (present on 1st and 2nd day only) |
| 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 | CHMP Representative |
| Vacant | EMA Representative |
| Vacant | EMA Representative |

**Observers:**

| | |
|---|---|
| Maria Mavris | Eurordis |

**European Commission:**

| | |
|---|---|
| Agnès Mathieu | DG Health and Consumers (present on 1st and 2nd day only) |

**EMA:**

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|---|---|
| Jordi Llinares Garcia | Head of Orphan Medicines |
| Stiina Aarum | Scientific Officer |
| Laura Fregonese | Scientific Officer |
| Segundo Mariz | Scientific Officer |
| Stylianos Tsigkos | Scientific Officer |
| Agnieszka Wilk-Kachlicka | Assistant |
| Frederique Dubois | Assistant |

# Apologies

**Members:**

| | |
|---|---|
| Aušra Matulevičienė | Lietuva |
| Henri Metz | Luxembourg |

**Observers:**

| | |
|---|---|
| Antonio Blazquez | Agencia Española de Medicamentos y Productos Sanitarios |