8 October 2013
EMA/COMP/366326/2013[1]
Human Medicines Development and Evaluation

Committee for Orphan Medicinal Products (COMP)

Minutes of the 9 - 11 July 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] Revision 1 following initial adoption at the September meeting. For first release following the October meeting.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu
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1. Introduction

1.1 Adoption of the agenda, EMA/COMP/366325/2013

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting on 11 - 13 June 2013, EMA/COMP/302197/2013

The minutes were adopted with minor corrections to points 5.2.2 and 5.3.15.

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:

- EGAN received a grant from the sponsor who have submitted dossier to be considered for review of orphan designation at the time of marketing authorisation (5.2.7). 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[2]

2.1. For opinion

2.1.1 Autologous regulatory T cells (Treg) with an immunophenotype of CD4+CD25hiFoxP3+ for prevention of rejection of solid organ transplantation, iReg Medical AB - EMA/OD/043/13

[Co-ordinators: K. Westermark / 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

With reference to the updated Guideline on Format and Content (ENTR/6283/00) the rationale for the use of the medicinal product in the orphan indication should be provided in this section. It should be noted that to support the rationale for the development of the product in the proposed condition, scientific evidence are generally required (literature data, preliminary results from preclinical or clinical studies) in the proposed condition.

To establish correctly if there exists a scientific rationale for the development of autologous regulatory T cells (Treg) with an immunophenotype of CD4+CD25hiFoxP3+ for prevention of rejection of solid organ transplantation, the sponsor should further discuss:

- the relevance of the model and of the results of the preclinical study of Treg in CBA mice receiving skin graft for the development of the product in the proposed condition (rejection of solid organ transplantation);

[2] 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 rationale and evidence for extrapolating to the proposed condition rejection of solid orphan transplantation the data from the cited published studies on graft versus host disease after bone marrow transplantation. In this respect it would also be needed to clarify whether the type of Tregs used in the abovementioned studies are the same as those being developed by the sponsor.

In addition the sponsor was invited to clarify which type of Treg the proposed product contains, i.e. whether they will use Treg generated by polyclonal stimulation of the T-cell receptor (CD3) or specifically activated by dendritic cells and how this might influence the expected activity of the product.

- Justification of significant benefit

The sponsor was requested to detail the results of any pre-clinical or clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of the condition. In particular, data supporting the reduced need for immunosuppressive therapy and reduced risk for transplant rejection would be of interest.

In the written response, and during an oral explanation before the Committee on 9 July 2013, the sponsor defended the validity of the preclinical studies on the grounds that the underlying immunological mechanism of allograft rejection is the same in almost all species. Furthermore, it was argued that the extrapolation from the cited clinical studies can be made on the basis of the two-way paradigm of transplantation immunology, which explains the bidirectional immunologic confrontation after transplantation (host-versus-graft, and graft-versus-host). With regards to the justification of significant benefit, the sponsor stressed that only 50% of solid organ transplant recipients retain functional allografts 10 years after transplantation with the current standard of care, and referred to the novel mechanism of action of the product that might be assumed to result in improved efficacy.

Following review of the application by the Committee, it was agreed to rename the indication as "prevention of graft rejection following solid organ transplantation".

The Committee agreed that the condition, graft rejection following solid organ transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing autologous regulatory T cells with an immunophenotype of CD4+CD25hiFoxP3+ was considered justified based on preclinical studies from the literature showing prevention of graft rejection in different models of solid organ transplantation.

The condition is chronically debilitating and life-threatening due to reduced function and survival of the transplanted organ. The population eligible for prevention was estimated to be approximately 0.6 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing autologous regulatory T cells with an immunophenotype of CD4+CD25hiFoxP3+ may be of significant benefit to the population at risk of developing the condition. The sponsor has provided and discussed preclinical data from the literature showing that administration of the proposed product in combination with the currently authorised immunosuppressive treatment resulted in prolonged survival of the transplanted organs as compared to immunosuppressive treatment alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous regulatory T cells with an immunophenotype of CD4+CD25hiFoxP3+, for prevention of graft rejection following solid organ transplantation, was adopted by consensus.

2.1.2 Octreotide acetate (oral use) for treatment of acromegaly, Larode Ltd - EMA/OD/042/13
[Co-ordinators: K. Westermark / 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

To establish correctly if there exists a scientific rationale for the development of octreotide acetate (oral use) for treatment of acromegaly, the sponsor was asked to further elaborate on:

- the role of the different components used as excipients in the junction-opening activity as described, and to which extent these components contribute to the pharmacodynamic of the product.

- Justification of significant benefit

The sponsor was invited to discuss the impact of the within subject variability measured in the repeated administration PK study on the claim of possible better efficacy of the proposed product vs. octreotide in the control of breakthrough symptoms.

In addition the sponsor was invited to present any available data from the ongoing phase III study to support a major contribution to patient care with the proposed product, such as improved convenience of use and/or quality of life.

In the written response, and during an oral explanation before the Committee on 9 July 2013, the sponsor discussed the composition of the proprietary excipient mix and explained the different roles of the single excipients in the junction-opening activity of the product, as requested by the Committee. The sponsor further elaborated on the pharmacokinetic data regarding the intestinal absorption of the proposed octreotide oral formulation vs. the currently widely used sub-cutaneous formulation. Written testimonials from clinicians were also presented, pointing towards an improved symptom control with the oral formulation. The on-going clinical trial was also further discussed.

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

The intention to treat the condition with the medicinal product containing octreotide acetate (oral use) was considered justified based on pharmacokinetic data showing a comparable availability to the currently authorized parenteral formulation of octreotide, and on clinical data showing suppression of growth hormone plasma levels after stimulation with growth hormone releasing hormone.

The condition is chronically debilitating due to abnormal growth of connective tissue, cartilage, bone, skin, and visceral organs. This results in increased morbidity and mortality due to cardiovascular, cerebrovascular, and respiratory disease. 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 octreotide acetate (oral use) may be of significant benefit to those affected by the condition. The sponsor provided data to support that there are serious and documented difficulties with the formulation or route of administration of the currently authorized octreotide products that are administered via intramuscular or subcutaneous route, e.g. pain and local reactions at the injection site. In addition, there is the need for the authorised products to be administered by healthcare professionals, requiring monthly visits to the hospital. The Committee considered that the possibility of

having an oral formulation of octreotide in alternative to the available parenteral formulations constitutes a major contribution to patient care for the patients affected by the condition.

A positive opinion for octreotide acetate (oral use) for treatment of acromegaly, was adopted by consensus.

2.1.3 Lipid-complexed cisplatin for treatment of osteosarcoma, Richardson Associates Regulatory Affairs Ltd - EMA/OD/020/13
[Co-ordinators: D. O'Connor / 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 lipid-complexed cisplatin for treatment of osteosarcoma, the sponsor was asked to further elaborate on:

- the relevance of the preclinical models used for the treatment of osteosarcoma, and the interpretation of the results obtained in the experiments;

- the full study report for the cited preliminary clinical study in patients affected by the proposed condition, clearly delineating the patients, assessments, responses and previous treatments.

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

- Justification of significant benefit

The arguments on significant benefit are based on the potential improved efficacy and improved safety in the condition.

The sponsor was asked to further elaborate and quantify these arguments, and position the product versus all satisfactory treatments without limiting the discussion to intravenous cisplatin.

In the written response, and during an oral explanation before the Committee on 9 July 2013, the sponsor further elaborated on the requested issues. Firstly, with regards the medical plausibility, the sponsor submitted the clinical study report as requested and provided a summary discussing in particular one patient who had a partial response after third line treatment and two cases where the patients remained without recurrence following metastectomy for the duration of the study. Secondly, with regards to the prevalence issue, the sponsor recalculated the estimate as incidence times duration. Thirdly, as for the significant benefit, the sponsor argued on the potential of improved efficacy, on the grounds of three patients that responded in third line treatment. The sponsor also discussed improved safety argued on the reduced systemic exposure of cisplatin.

The COMP considered that the medical plausibility may be accepted based on the preliminary clinical data and that the prevalence is in line with the previous considerations of the Committee. It was also

considered that even though the available clinical data are very preliminary, they suggest some effects in a population for which there are no clear treatment recommendations and for whom limited options exist. Therefore, the significant benefit may be accepted on the grounds of improved efficacy in this population.

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

The intention to treat the condition with the medicinal product containing lipid-complexed cisplatin was considered justified based on preliminary clinical data showing favourable effects in osteosarcoma patients with lung metastases.

The condition is chronically debilitating due to the potential of limb amputation and life-threatening with a less than a 20% long-term survival rate following recurrence. The condition was estimated to be affecting less than 2.5 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 lipid-complexed cisplatin may be of significant benefit to those affected by the condition. This was based on preliminary clinical data showing responses in osteosarcoma patients with lung metastases that have relapsed following previous treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for lipid-complexed cisplatin for treatment of osteosarcoma, was adopted by consensus.

2.1.4 Product for prevention of recurrent hepatitis C virus induced liver disease in liver transplant recipients -EMA/OD/050/13 *[Co-ordinators: N. Sypsas / 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 indication

The sponsor was asked to reword the proposed indication to "prevention of recurrent hepatitis C in liver transplant recipients", and justify the intention to "prevent" rather than treating the proposed condition.

- Medical plausibility

To establish correctly if there exists a scientific rationale for prevention of recurrent hepatitis C in liver transplant recipients, the sponsor was invited to further elaborate on:

- the prevention or treatment articulation of the indication, given that studies presented as proof of concept describe biochemical effects in chronic hepatitis patients;

- the absence of any preclinical or clinical proof of concept in the specific condition proposed for designation, which is HCV hepatitis recurrence in liver transplant recipients;

- the results from the preliminary clinical studies vis a vis the proposed indication as applied for designation.

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

The sponsor was requested to re-calculate the prevalence estimate based on the specific population the orphan designation is sought in.

In the written response, and during an oral explanation before the Committee on 10 July 2013, the sponsor clarified the scope of the sought indication and reworded the proposed orphan indication to: "treatment of recurrent hepatitis C induced liver disease in liver transplant recipients".

The sponsor also elaborated on the similar features of the chronic HCV population and in the sought indication, in an effort to extrapolate the biochemical effects seen in chronic HCV patients to draw conclusions for the proposed orphan indication.

The Committee considered that recurrence of HCV in LT recipients is a distinct entity compared to chronic HCV in non-transplant recipients, and that the biochemical endpoints discussed do not allow for an extrapolation to the sought indication and the justification of the medical plausibility.

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

2.1.5 Product for treatment of snakebite envenomation- EMA/OD/068/13

[Co-ordinators: I. Kkolos / 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

To establish correctly if there exists a scientific rationale for the treatment of snakebite envenomation, the sponsor was invited to present data (e.g. from literature) regarding the efficacy of the proposed product in snakebite envenomation. In case the sponsor aimed at presenting data using other products, extrapolation of the data of these products to the proposed product should be discussed and justified.

The sponsor was also invited to discuss and substantiate the specificity and para-specificity of the product especially in sub-species of the *Viperidae* family not mentioned in the application but existing in the European Union, e.g. *Macrovipera lebetina lebetina.*

- Justification of significant benefit

The sponsor was invited to support with data the claimed availability issue with products for snakebite envenomation in the EU, in line with what requested by the Communication from the Commission on Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products (quote: "*If the argument for significant benefit is based on an increase in supply/availability of the method, the sponsor must provide details of the supply/availability problem and explain why this results in the unmet needs of patients. All claims should be substantiated by qualitative and quantitative references. If the supply of existing methods is sufficient to meet patients' needs in the orphan indication an increase in supply will not be viewed as a significant benefit*")

Similarly, the sponsor was invited to discuss the clinical relevance of the results of the neutralization assay to an assumed clinically relevant advantage of the product as compared to what already authorized in the EU for the treatment of the condition.

Finally the sponsor was invited to elaborate on the methods for the purification of the product and on how this would translate into a safer profile as claimed.

In the written response, and during an oral explanation before the Committee on 9-10 July 2013, the sponsor further elaborated on the medical plausibility by referring to clinical data with other products that the sponsor produces for extra-European regions. The sponsor also elaborated on the justification of significant benefit by stressing that authorised products with the same mode of action are available in only three EU member states.

The Committee considered that the sponsor had not addressed the specificity and paraspecificity of the the product as requested with regards to sub-species of the Viperidae family and in particular the Macrovipera lebetina lebetina which is found in Cyprus. The COMP also considered that the sponsor has not documented the lack of availability of authorised products in the EU, and it was pointed out that Croatian products have not been taken into consideration in the sponsor's discussion.

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

2.1.6 **Tolvaptan** for treatment of autosomal dominant polycystic kidney disease, Otsuka Pharmaceutical Europe Ltd - EMA/OD/066/13

[Co-ordinators: A. Corrêa Nunes / 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:

- Prevalence

The sponsor has based the prevalence calculation on two publications and the ERA-EDTA registry data. The sponsor was invited to further clarify the exclusion criteria of the majority of the over 2,700 publications.

The disease is diagnosed based on imaging and symptoms are thus not always present. Some patients are diagnosed based on the suspicion triggered by a family history. Subsequently it is necessary to add a number of cases asymptomatic patients to every index case.

Also, the diagnosis rate that is applied is crucial for the calculation. Neumann et al. refers to a rate of 90% whereas Davis uses a rate 80%. The sponsor should further substantiate and justify the use of the chosen diagnosis rate. The sponsor is also invited to provide sensitivity analyses consistently using different diagnosis rates.

With regards to the registry data, the sponsor should clarify how the data on the prevalence of ADPKD has been inferred.

Finally, the sponsor was asked to comment the following statement by Neumann et al: "it is highly likely that the data for the 50-59 age group, where maximal penetrance is achieved, represent the prevalence data very close to the truth".

In the written response, and during an oral explanation before the Committee on 10 July 2013, the sponsor reiterated the methodology used. As regards the population-based studies 7 references have

been shortlisted, but only two were considered as valid. With regards to the requested sensitivity analysis, the sponsor varied the diagnostic rate of ADPK (to account for asymptomatic patients), up to the extent of 80%. Moreover, in order to validate the renal registry data, they compared and contrasted to the population based studies; similar but lower estimates were calculated this way. Finally the sponsor attributed the quote from the Neumann paper to the difference between the prevalence of the underlying mutations and the prevalence of the clinical condition.

The Committee considered that Overall the sponsor has performed a thorough review of the available literature studies on the issue. There was a discussion pertaining to the extent that asymptomatic patients may be taken into account for the calculation of prevalence for the proposed condition. The Committee also reflected on whether genotype would be reliable for the purpose of calculation, but concluded that having the genotype is a risk for developing the condition and therefore different from having the condition; hence it may not be used alone for the calculation of prevalence of the condition as applied for designation.

The Committee accepted the sensitivity analysis of the sponsor and concluded at an approximately 4/10,000 prevalence figure. The Committee also stressed that at the time of marketing authorisation, a thorough examination of, inter alia, the prevalence criterion will have to be performed.

The Committee agreed that the condition, autosomal dominant polycystic kidney disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing tolvaptan was considered justified based on preliminary clinical data showing that tolvaptan, as compared with placebo, slowed the increase in total kidney volume and the decline of kidney function over a 3-year period in treated patients affected by the condition.

The condition is chronically debilitating and life-threatening in particular due to the development of kidney failure, cardiovascular abnormalities and diverticulitis. The condition was estimated to be affecting approximately 4 in 10,000 people in the European Union, at the time the application was made; this was based on current data from literature and renal registries;

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 tolvaptan, for treatment of autosomal dominant polycystic kidney disease, was adopted by consensus.

2.1.7 Product for treatment of systemic transthyretin-related amyloidosis- EMA/OD/049/13

[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:

- 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 was asked to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition, and clearly describe and justify the methodology used for the prevalence calculation.

In addition, the sponsor was invited to re-calculate the prevalence estimate based on relevant epidemiological studies or registers and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was advised to perform a sensitivity analysis of the reported calculations.

- Justification of significant benefit

The arguments on significant benefit are based on the potential of improved efficacy. The sponsor was invited to further elaborate on the claims of significant benefit by taking into consideration that:

- the proposed product is argued to have the same mechanism of action as the authorised counterpart;

- the fact that different potencies do not translate per se in different efficacy profiles.

The sponsor was requested to detail the results of any 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 10 July 2013, the sponsor re-calculated the prevalence for ATTR-amyloidosis based on the sum of three clinical phenotypes (polyneuropathy, cardiomyopathy and senile).

As regards the significant benefit argumentation, the sponsor argued that the product has additional properties compared to the authorised product, relating to "the disruption of pre-existing fibrils". This was argued on the basis of assays of in vitro disruption of pre-formed fibrils. The sponsor was unable to establish the relevance of this additional property in the clinical setting of the condition. The COMP was of the opinion that the in vitro data while interesting was not robust enough at this stage to support the assumption of significant benefit.

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

2.1.8 Idelalisib for treatment of nodal marginal zone lymphoma - EMA/OD/054/13 and for treatment of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma) – EMA/OD/105/13 and for treatment of splenic marginal zone lymphoma - EMA/OD/106/13, Gilead Sciences International Ltd
[Co-ordinators: B. Dembowska-Bagińska / 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 orphan condition

As per the current WHO classification, the proposed condition as applied for designation comprises three distinct medical entities, namely splenic marginal zone lymphoma, nodal marginal zone lymphoma, and extra nodal marginal zone lymphoma of mucosa-associated lymphoid tissue.

The sponsor was invited to apply for the underlying entities separately.

- Seriousness

The sponsor was invited, in light of the amended indications to justify the chronically debilitating and/or life-threatening nature of each condition separately.

- 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".

In light of the amended indications the sponsor was asked to recalculate the prevalence estimate based on relevant epidemiological studies and registers.

In the written response, the sponsor accepted the WHO classification and submitted three new application forms for the three conditions as requested. The seriousness was addressed separately, and the prevalence calculated from the 2008 NHL Globocan prevalence, adjusted for the ratio of 0.8% for splenic, 1.8% for nodal, and 7.6% for MALT lymphoma, the ratios based on a 15 year old publication. Given the paucity of data these estimates were considered acceptable by the Committee.

Treatment of nodal marginal zone lymphoma

Following review of the application by the Committee, it was agreed to rename the indication as "treatment of nodal marginal zone lymphoma".

The Committee agreed that the condition, nodal marginal zone lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing idelalisib was considered justified based on preliminary clinical studies in patients with relapsed or refractory marginal zone lymphoma that responded to treatment.

The condition is life-threatening and chronically debilitating due to lymphadenopathy, systemic symptoms such as night sweats and weight loss and the potential of transformation to aggressive lymphoma. The condition was estimated to be affecting approximately 0.1 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 idelalisib may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that patients with marginal zone lymphoma who have relapsed or are refractory to the currently available products respond to treatment with idelalisib. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for idelalisib, for treatment of nodal marginal zone lymphoma, was adopted by consensus.

Treatment of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Following review of the application by the Committee, it was agreed to rename the indication as "treatment of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)".

The Committee agreed that the condition, extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing idelalisib was considered justified based on preliminary clinical studies in patients with relapsed or refractory marginal zone lymphoma that responded to treatment.

The condition is life-threatening and chronically debilitating due to gastric manifestations such as dyspepsia, epigastric pain, and nausea, the potential of bone marrow involvement and of transformation to aggressive lymphoma. The condition was estimated to be affecting approximately 0.4 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 idelalisib may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that patients with marginal zone lymphoma who have relapsed or are refractory to the currently available products respond to treatment with idelalisib. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for idelalisib, for treatment of extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma), was adopted by consensus.

Treatment of splenic marginal zone lymphoma

Following review of the application by the Committee, it was agreed to rename the indication as "treatment of splenic marginal zone lymphoma".

The Committee agreed that the condition, splenic marginal zone lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing idelalisib was considered justified based on preliminary clinical studies in patients with relapsed or refractory marginal zone lymphoma that responded to treatment.

The condition is life-threatening and chronically debilitating due to splenomegaly, bone marrow involvement and the potential of transformation to aggressive lymphoma. The condition was estimated to be affecting approximately 0.05 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 idelalisib may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing that patients with marginal zone lymphoma who have relapsed or are refractory to the currently available products respond to treatment with idelalisib. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for idelalisib, treatment of splenic marginal zone lymphoma, was adopted by consensus.

2.1.9 Idelalisib for treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma, Gilead Sciences International Ltd - EMA/OD/056/13
[Co-ordinators: B. Dembowska-Bagińska / 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:

- 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 was asked to justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition

As it seems that the sponsor has excluded part of the population affected by the condition the sponsor was invited to indicate on which population the prevalence calculation is based on.

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

In the written response, the sponsor further elaborated on the prevalence of the proposed condition as requested.

Following review of the application by the Committee, it was agreed to rename the indication "treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma".

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 was considered justified based on based on preliminary clinical studies in patients with relapsed or refractory disease that responded to treatment.

The condition is life-threatening and chronically debilitating due to development of cytopenias (anaemia, neutropenia, thrombocytopenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections. The condition was estimated to be affecting less than 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 idelalisib 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 idelalisib. The Committee considered that this constitutes a clinically relevant advantage.

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

2.1.10 *Trans-N1-((1R,2S)*-2-phenylcyclopropyl)cyclohexane-1,4-diamine bis-hydrochloride

for treatment of acute myeloid leukaemia, Oryzon Genomics SA - EMA/OD/064/13
[Co-ordinators: B. Dembowska-Bagińska / 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:

- Justification of significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preclinical study where their product was used on its own or in combination with other epigenetic therapies 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 9-10 July 2013, the sponsor further elaborated on the issue of significant benefit. In particular, the sponsor highlighted the current treatments for the proposed condition in the context of ESMO guidelines and argued that there is no consensus on a single 'best' post-remission treatment strategy. The COMP was of the opinion the new mode of action may have the potential for improved efficacy compared to currently available treatments, as supported by the preclinical data presented in the application.

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 *trans-N1-((1R,2S)*-2-phenylcyclopropyl)cyclohexane-1,4-diamine bis-hydrochloride was considered justified based on preclinical in vivo data where the product has shown that there was an inhibition of the tumour progression.

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 2.7 in 10,000 people in the European Union, at the time the application was made; the sponsor has based their calculation in the EUCAN registry and a literature search.

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 *trans-N1-((1R,2S)*-2-phenylcyclopropyl)cyclohexane-1,4-diamine bis-hydrochloride may be of significant benefit to those affected by the condition. The sponsor has provided preclinical in vivo models which supported the inhibition of tumour progression through a new mode of action targeting lysine-specific demethylase 1 thereby offering an alternative approach in the treatment of relapsed or refractory acute myeloid leukaemia. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for *trans-N1-((1R,2S)*-2-phenylcyclopropyl)cyclohexane-1,4-diamine bis-hydrochloride, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.1.11 Product for treatment of small cell lung cancer - EMA/OD/040/13
[Co-ordinators: K. Kubáčková / 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

Pre-clinical

To establish correctly if there exists a scientific rationale for the development for treatment of small cell lung cancer, the sponsor is invited to:

- discuss the plausibility and clinical relevance of studying the combination in animal models for the treatment of small cell lung cancer;

- integrate the pre-clinical data on xenograft models of SCLC with the results immunotherapy. This is needed in order to evaluate the effects used in monotherapy in animal models and the magnitude of the effects resulting from the combination discuss the effects of the product as a monotherapy and as a combination therapy, in relation to the effects of authorised products in the same pre-clinical models.

Clinical

To establish correctly if there exists a scientific rationale for treatment of small cell lung cancer, the sponsor is invited to:

- describe more in details the methodology of the phase I/II trial in patients with small cell lung cancer, including e.g. the type of pre-treatment of patients who had what the sponsor calls "resistant relapse". The sponsor is also invited to clarify the concept of "resistant relapse" in this context;

- discuss the clinical relevance of the phase I/II study results with the product as a monotherapy in small cell lung cancer, also taking into account that the planned development seems to foresee only studies in combination with other products.

- Justification of significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and in particular what is the assumed clinically relevant advantage of the product as compared to what is already authorized for the treatment of the condition.

When the intended use as a monotherapy, the sponsor is invited to substantiate with data and numbers the statement that "*these data are comparable to historical data with standard treatment topotecan or other accepted second line agents in this setting*".;

When the intended use is in combination, the sponsor is invited to provide data in small cell lung cancer showing that the combination results in preliminary evidence of significant benefit as compared to what already authorized for the treatment of the condition.

- Development of the product

The sponsor indicated that the product will be used in clinical studies as a combination treatment. The sponsor is invited to elaborate on this.

The Committee was informed that the sponsor withdrew the application on 21 June 2013, prior to responding to the list of questions.

2.1.12 Product for treatment and management of squamous cell carcinoma of the head and neck, in combination with chemotherapy - EMA/OD/048/13
[Co-ordinators: A. Magrelli / 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:

- Orphan indication

The sponsor is reminded that according to Regulation (EC) No 141/2000 a medicinal product is "*intended for the diagnosis, prevention or treatment*" of a condition, therefore the word "management" is not acceptable as part of the wording of the orphan indication.

- Medical plausibility

Squamous cell carcinoma of the head and neck in combination with chemotherapy is not perceived by the Committee as a valid subset.

Squamous cell carcinoma of the head and neck in combination with chemotherapy should be justified as a distinct medical entity or a valid subset, or the application should be changed accordingly. 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).

To this aim, the sponsor is reminded of the definition of a subset:

"*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 particular, the pathophysiological characteristics associated with this subset should be closely linked to the pharmacological action of the medicinal product in such a way that the absence of these characteristics will render the product ineffective in the rest of the population*"

It is apparent that the product will be used only in combination with chemotherapy. In this respect the sponsor is invited to discuss:

- the possible use with chemotherapic antineoplatic agents other than cisplatin;

- the subset's distinct and unique evaluable characteristics with a plausible link to the condition;

- the link between the pharmacological action of the product and the proposed subset.

In addition, in order to establish correctly if there exists a scientific rationale for the development for the treatment of squamous cell carcinoma of the head and neck, in combination with chemotherapy, the sponsor should further discuss:

- the antineoplastic activity of the produced substance when used as single agent;

- the results of the Phase I study where no significant difference was detected between the remission rate of patients treated with chemotherapy alone vs. chemotherapy combined with the proposed product;

- the results of the Phase II study in patients with local recurrent or metastatic head and neck squamous cell carcinoma where no statistically significant difference in overall survival was detected between chemotherapy alone and chemotherapy combined with the proposed product;

- the choice of endpoints such as progression free survival and time to progression in the phase II trial, for studying a population that is heterogeneous in terms of previous treatment regimens and tumour stage.

- Prevalence

The sponsor has excluded part of the population affected by squamous cell carcinoma of the head and neck based on the intended use of the product (in combination with chemotherapy). As this is not perceived by the Committee as a valid subset, the sponsor is invited to conclude on the prevalence of the broad condition squamous cell carcinoma of the head and neck rather than on the prevalence of the proposed subset.

For this purpose, the sponsor is reminded that complete prevalence is needed rather than 5-year prevalence.

The Committee was informed that the sponsor withdrew the application on 20 June 2013, prior to responding to the list of questions.

2.1.13 Product for treatment of prurigo nodularis, EMA/OD/046/13
[Co-ordinators: J. Torrent-Farnell / 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

In the absence of data with the specific product in the applied condition the Committee will not consider that the intention to treat is justified. To establish correctly if there exists a scientific rationale for the treatment of prurigo nodularis, the sponsor should further elaborate on:

- the relevance of the preclinical model of foot tapping used, for the treatment of prurigo nodularis, and the interpretation of the results obtained in the experiments, given the anxiolytic and preventive characteristics of the settings;

- the bridging with the effects of other products with similar pharmacological properties, in the clinical setting of the condition as proposed for designation, given the uncontrolled nature of the clinical studies discussed and the fact that they do not pertain to the substance proposed for designation;

- the absense of any data in either preclinical or clinical settings with the specific product of this application in the specific condition as applied for designation.

- 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 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.

Moreover, a calculation based on the number of patients affected by the underlying primary disorders (that initiate the itching-scratching cycle and ultimately result in prurigo nodularis) should be submitted in order to clarify the situation.

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy in the condition. The sponsor is requested to further discuss the arguments provided for significant benefit and substantiate this by any data in relevant preclinical models or preliminary clinical settings.

The Committee was informed that the sponsor withdrew the application on 20 June 2013, prior to responding to the list of questions.

2.2. For discussion / preparation for an opinion

2.2.1 (1R,3R,4R,5S)-3-O-[2-O-benzoyl-3-O-(sodium(2S)-3-cyclohexyl-propanoate-2-yl)-β-D-galactopyranosyl]-4-O-(α-L-fucopyranosyl)-5-orothylamido-cyclohexane-1-carboxylic acid (ethyl-2-amidyl-ethyloxy-2-acetyl-(8-amino-1,3,6-naphthalene-tris sodium sulfonate) amide

(1R,3R,4R,5S)-3-O-[2-O-benzoyl-3-O-(sodium(2S)-3-cyclohexyl-propanoate-2-yl)-β-D-galactopyranosyl]-4-O-(α-L-fucopyranosyl)-5-orothylamido-cyclohexane-1-carboxylic acid (ethyl-2-amidyl-ethyloxy-2-acetyl-(8-amino-1,3,6-naphthalene-tris sodium sulfonate) amide for treatment of sickle cell disease, Pfizer Limited - EMA/OD/084/13
[Co-ordinators: V. Stoyanova / L. Fregonese]

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

The intention to treat the condition with the medicinal product containing (1R,3R,4R,5S)-3-O-[2-O-benzoyl-3-O-(sodium(2S)-3-cyclohexyl-propanoate-2-yl)-β-D-galactopyranosyl]-4-O-(α-L-fucopyranosyl)-5-orothylamido-cyclohexane-1-carboxylic acid (ethyl-2-amidyl-ethyloxy-2-acetyl-(8-amino-1,3,6-naphthalene-tris sodium sulfonate) amide was considered justified based on preclinical data showing improvement of blood flow and on preliminary clinical data showing reduction of the time to resolution of vaso-occlusive crisis in patients treated with the proposed product.

The condition is life-threatening and chronically debilitating due to haemolytic anaemia, and to painful vaso-occlusive crisis with ischemia-reperfusion injury of bone, muscle, or internal organs. This leads to fever, abdominal pain, leg ulcers, aseptic necrosis, and eye damage. Acute chest syndrome may also occur. The condition was estimated to be affecting approximately 1.5 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 (1R,3R,4R,5S)-3-O-[2-O-benzoyl-3-O-(sodium(2S)-3-cyclohexyl-propanoate-2-yl)-β-D-galactopyranosyl]-4-O-(α-L-fucopyranosyl)-5-orothylamido-cyclohexane-1-carboxylic acid (ethyl-2-amidyl-ethyloxy-2-acetyl-(8-amino-1,3,6-naphthalene-tris sodium sulfonate) amide may be of significant benefit to those affected by the condition. The sponsor provided preliminary clinical data showing reduction of the duration of vaso-occlusive crisis in patients already treated with the currently authorized medicinal product for this condition. The possibility of using the product in combination with the current treatment for the acute treatment of vaso-occlusive crisis represents a clinically relevant advantage for the subjects affected by the condition.

The COMP recommends that protocol assistance is sought from the EMA prior to submission of the application for marketing authorisation, particularly with regard to the clinical development and the data that will be required for the demonstration of significant benefit.

A positive opinion for (1R,3R,4R,5S)-3-O-[2-O-benzoyl-3-O-(sodium(2S)-3-cyclohexyl-propanoate-2-yl)-β-D-galactopyranosyl]-4-O-(α-L-fucopyranosyl)-5-orothylamido-cyclohexane-1-carboxylic acid

(ethyl-2-amidyl-ethyloxy-2-acetyl-(8-amino-1,3,6-naphthalene-tris sodium sulfonate) amide, for treatment of sickle cell disease, was adopted by consensus.

2.2.2 Apremilast for treatment of Behçets' disease, Celgene Europe Limited - EMA/OD/076/13
[Co-ordinators: V. Saano / S. Aarum]

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

The intention to treat the condition with the medicinal product containing apremilast was considered justified based on preliminary clinical data in patients affected by the condition showing that treatment with the product reduces the number of oral ulcers.

The condition is chronically debilitating, in particular due to widespread vasculitis of the arteries and veins of any size or thrombophilia, leading to painful mucocutaneous and genital ulcers, skin lesions, ocular inflammation that may lead to blindness, arthritis, thromboembolic vascular complications, neurological, pulmonary, gastrointestinal, renal and genito-urinary manifestations. 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 apremilast may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients affected by the condition showing that treatment with the product reduces the counts of oral ulcers. The results compare favourably with bibliographical studies for authorised counterparts, justifying an assumption of improved efficacy. The Committee considered that this constitutes a clinically relevant advantage.

Protocol assistance in particular with regards to the demonstration of significant benefit at the Marketing authorisation stage is recommended.

A positive opinion for apremilast, for treatment of Behçets' disease, was adopted by consensus.

2.2.3 Budesonide for treatment of eosinophilic esophagitis, Dr Falk Pharma GmbH - EMA/OD/078/13
[Co-ordinators: A. Lhoir / L. Fregonese]

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

The intention to treat the condition with the medicinal product containing budesonide was considered justified based on clinical trials from the literature showing histologic response and reduction of symptoms in adult and paediatric patients treated with budesonide.

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 budesonide, for treatment of eosinophilic esophagitis, was adopted by consensus.

2.2.4 Chimeric monoclonal antibody against claudin-18 splice variant 2 for treatment of pancreatic cancer, GANYMED Pharmaceuticals AG - EMA/OD/071/13
[Co-ordinators: B. Bloechl-Daum / S. Mariz]

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

The intention to treat the condition with the medicinal product containing chimeric monoclonal antibody against claudin-18 splice variant 2 was considered justified based on preclinical in vivo data with pancreatic cancer cells expressing claudin 18 where an inhibition in tumour growth and improved survival were seen.

The condition is life-threatening with a 1-year relative survival rate of 25%, and a 5-year survival estimated as less than 5% for all forms. The condition was estimated to be affecting approximately 1.1 in 10,000 people in the European Union, at the time the application was made; this was established using the Globocan 2008 registry.

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 chimeric monoclonal antibody against claudin-18 splice variant 2 may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo data using pancreatic tumour cells expressing claudin 18 splice variant 2. They have shown that there was an inhibition of tumour growth and improved survival when the product was used in combination with gemcitabine. The Committee considered that the assumption of a clinically relevant advantage has been justified.

The COMP recommends that protocol assistance is sought from the EMA prior to submission of the application for marketing authorisation, particularly with regard to the clinical development and the data that will be required for the demonstration of significant benefit.

A positive opinion for chimeric monoclonal antibody against claudin-18 splice variant 2, for treatment of pancreatic cancer, was adopted by consensus.

2.2.5 Cladribine for treatment of mastocytosis, Lipomed GmbH - EMA/OD/079/13
[Co-ordinators: B. Dembowska-Bagińska / L. Fregonese]

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

The intention to treat the condition with the medicinal product containing cladribine was considered justified based on clinical studies from the literature showing overall response rates up to 72% in systemic mastocytosis with reduction of clinical signs and symptoms, including when the product is used in first line.

The condition is chronically debilitating due to symptoms caused by release of histamine and tryptase by the tumour cells, including flushing, tachycardia, pruritus, abdominal cramping, peptic ulcer

disease, and diarrhoea. Infiltration of various organs by malignant cells in aggressive forms can be life-threatening, due to bone marrow failure, hepatomegaly with ascites and impaired liver function, splenomegaly with hypersplenism. Five-year survival rate is around 61% in systemic mastocytosis. The condition was estimated to be affecting approximately 2.6 in 10,000 people in the European Union, at the time the application was made, based on a literature search.

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 cladribine may be of significant benefit to those affected by the condition. Cladribine kills the tumour cells, while the only currently authorized product for the treatment of mastocitosis in the EU just acts on one or more symptoms of the condition. The sponsor supported the significant benefit with bibliographic clinical evidence showing good response in systemic mastocitosis in terms of overall response rates, progression free survival, time to progression, and clinical signs and symptoms. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by mastocytosis.

The COMP recommends that protocol assistance is sought from the EMA prior to submission of the application for marketing authorisation, particularly with regard to the clinical development and the data that will be required for the demonstration of significant benefit.

A positive opinion for cladribine, for treatment of mastocytosis, was adopted by consensus.

2.2.6 Product for the treatment of glioma - EMA/OD/033/13

[Co-ordinators: D. O'Connor / 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 in the treatment of glioma, the sponsor should further elaborate on:

- the relevance of the results obtained with the product in the in vitro glioblastoma cell line studies that have been presented to the clinical condition.

Non-clinical data should be discussed in full and in particular the sponsor should further discuss the concentrations used and how this corresponds to the potential doses which could have an effect in the clinical setting.

The sponsor should also discuss how a combination therapy with the proposed product could be translated into use in the clinical setting.

The lack of data from a relevant in vivo model should be justified by the sponsor.

- Prevalence

The sponsor should re-calculate the prevalence estimate based on additional more extensive use of relevant epidemiological studies and registers for the proposed orphan condition.

- 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 in vitro studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

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 September meeting.

2.2.7 Eculizumab for treatment of neuromyelitis optica, Alexion Europe SAS –EMA/OD/087/13 (active time: day 34)
[Co-ordinators: A. Magrelli / S. Tsigkos]

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

The intention to treat the condition with the medicinal product containing eculizumab was considered justified based on preliminary clinical data showing a reduction in the number of relapses in patients treated with the product.

The condition is chronically debilitating due to neurological impairment such as paraplegia, sensory loss, bladder dysfunction, and central visual loss accompanied by ocular pain, and life-threatening with 5-year mortality reported as high as 30%. The condition was estimated to be affecting approximately 0.4 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.

The COMP recommends that protocol assistance is sought from the EMA.

A positive opinion for eculizumab, for treatment of neuromyelitis optica, was adopted by consensus.

2.2.8 Human allogeneic bone marrow derived osteoblastic-like cells for treatment of non-traumatic osteonecrosis, Bone Therapeutics SA - EMA/OD/070/13
[Co-ordinators: A. Corrêa Nunes / S. Mariz]

The Committee agreed that the condition, non-traumatic osteonecrosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing human allogeneic bone marrow derived osteoblastic-like cells was considered justified based on pre-clinical in vivo data which showed that the product induces bone repair and can enhance bone engraftment.

The condition is chronically debilitating due to pain and limitation of movement extending to all directions of the affected joint progressing to functional incapacity. The condition was estimated to be affecting 2.9 in 10,000 people in the European Union, at the time the application was made; this was based on a review of scientific literature.

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 allogeneic bone marrow derived osteoblastic-like cells, for treatment of non-traumatic osteonecrosis, was adopted by consensus.

2.2.9 Product for treatment of chronic sarcoidosis - EMA/OD/081/13
[Co-ordinators: L. Gramstad / L. Fregonese]

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 in the treatment of chronic sarcoidosis, the sponsor should further elaborate on:

- the reasons for seeking the designation of chronic sarcoidosis rather than sarcoidosis as a whole;

- the relevance of the results obtained in animal models of sciatic crush injury, spared nerve injury, and neuro-inflammation induced by Freund's adjuvant to the specific neuro-inflammation described in sarcoidosis;

- the relevance of neuropathic pain to the clinical setting of sarcoidosis;

- the relevance of the endpoints of the phase II clinical trial to the treatment of sarcoidosis;

- any results other than on neurological endpoints from the phase II study.

- Justification of significant benefit

The sponsor is invited to further discuss the grounds supporting significant benefit, i.e. the clinically relevant advantage or major contribution to patient care that the proposed product would bring in comparison to what is already authorized for the treatment of the proposed condition.

In this respect the sponsor is also invited to further discuss the methodology and results of the phase II trial, including the use of concomitant treatments.

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

2.2.10 Product for treatment of myotonic disorders - EMA/OD/069/13
[Co-ordinators: I. Bradinova / S. Mariz]

Following review of the application by the Committee, it was agreed that the proposed indication comprises two distinct medical entities, namely dystrophic myotonia and non-dystrophic myotonia. The Committee requested the applicant to amend the proposed indication and submit two applications for the two conditions. In case the applicant had reservations, they were invited to an oral explanation before the Committee at the September meeting.

Post meeting note:

Following the Sponsor's request, a list of issues was sent to the sponsor on 13 August 2013.

The Committee considered that the following issues have to be discussed with the sponsor:

- Proposed indication

In the sponsor's application, it is asserted that: "…Dystrophia myotonica [Steinert], Myotonia congenita and Paramyotonia congenita are subgroups of the myotonic disorders. Dystrophia myotonica is characterized by the presence of myotonic phenomenon and muscular dystrophy, whereas in myotonia and paramyotonia congenita muscular dystrophy is absent or very limited and secondary to the persistence of the myotonic phenomenon…"

Therefore more than one distinct medical entity is considered in this application. At this point, the attention of the sponsor is drawn to the updated guideline ENTR/6283/00 Rev 03 that states that "If more than one indication is applied for the same product, separate applications should be submitted for each indication".

The sponsor is hence invited to amend the proposed indication by submitting two separate applications for a) treatment of dystrophic myotonia and b) treatment of non-dystophic myotonia. Updated application forms and scientific annexes are to be submitted for the abovementioned indication, including inter alia a *separate prevalence estimate* (emphasis added) for each of them.

2.2.11 PEGylated Recombinant Anti-*Pseudomonas aeruginosa* PcrV Fab' Antibody for treatment of Pseudomonas aeruginosa lung infection in cystic fibrosis, KaloBios Ltd - EMA/OD/073/13 *[Co-ordinators: V. Saano / L. Fregonese]*

The Committee agreed that the condition, *Pseudomonas aeruginosa* lung infection in cystic fibrosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing PEGylated recombinant anti-*Pseudomonas aeruginosa* PcrV Fab' antibody was considered justified based on preclinical data showing almost 100% survival in a model of lethal infection, together with reduction of airway infection and inflammation. The reduction of airway inflammation was confirmed in a clinical study in patients affected by *Pseudomonas aeruginosa* lung infection in cystic fibrosis.

The condition is chronically debilitating due to the chronic inflammation of the infected airways leading to cystic fibrosis exacerbations and progressive damage of the airway walls. The condition is life-threatening due to the development of bronchiectasis in the chronically inflamed airways, with possible erosion of the bronchial wall and haemoptysis due to rupture of pulmonary vessels. The condition was estimated to be affecting less than 0.6 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing PEGylated recombinant anti-*Pseudomonas aeruginosa* PcrV Fab' antibody may be of significant benefit to those affected by the condition. The product has a novel mechanism of action targeting the protein that enables *Pseudomonas aeruginosa* to attack and kill the host cell. The sponsor provided experimental models and clinical data in cystic fibrosis, showing reduction of airway infection and inflammation induced by *Pseudomonas aeruginosa*. The activity of the product was enhanced when used in combination with tobramycin, currently authorized for the treatment of the condition. The possibility of targeting *Pseudomonas aeruginosa* lung infection in cystic fibrosis in a new way from what already authorized for this condition, together with data showing the efficacy of the product alone and in combination with tobramycin constitutes a clinically relevant advantage for the patient population affected by the condition.

The COMP recommends that protocol assistance is sought from the EMA prior to submission of the application for marketing authorisation, particularly with regard to the clinical development and the data that will be required for the demonstration of significant benefit

A positive opinion for Pegylated recombinant anti-*Pseudomonas aeruginosa* PcrV Fab' antibody, for treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis, was adopted by consensus.

2.2.12 Product for treatment of cervical insufficiency EMA/OD/085/13
[Co-ordinators: K. Westermark / S. Tsigkos]

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

- Proposed indication

The sponsor is invited to provide an **internationally established and agreed upon definition** (emphasis added) of the proposed condition as applied for designation. Without such a definition of a valid condition for designation, the Committee cannot consider whether the criteria for orphan designation are fulfilled.

- Medical plausibility

The sponsor defends the medical plausibility on the basis of clinical studies showing protection against preterm birth in patients with 'short cervix' compared to placebo.

To establish correctly if there exists a scientific rationale for the development in the treatment of cervical insufficiency, the sponsor should further elaborate on the use of 'short cervix' measured with trans vaginal ultrasound as a surrogate to draw conclusions for the proposed condition as applied for designation, which is cervical insufficiency.

Moreover the sponsor should clarify if the product is proposed for the treatment of short cervix, treatment of cervical insufficiency, or prevention of preterm birth.

- 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 further elaborate on the duration of the proposed condition as applied for designation.

- The sponsor should elaborate on the epidemiological consequences of the fact that there is no agreed definition of the condition as applied for designation, and discuss alternative calculations based on different approaches that focus on structural or functional aspects.

- An additional calculation based on the sum of underlying disorders that cause the condition is also invited.

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 September meeting.

2.2.13 Product for treatment of congenital factor VII deficiency - EMA/OD/051/13
[Co-ordinators: L. Gramstad / S. Tsigkos]

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

- Justification of significant benefit

The arguments on significant benefit are based on improved pharmacokinetics compared to the authorised counterparts.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the clinical benefit of the proposed improved pharmacokinetics with regards to the

potential dosing scheme for patients affected by the condition, in the context of the current treatment practice of factor VII deficiency.

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 September meeting.

2.2.14 Recombinant human growth hormone modified by fusion with two hydrophilic polypeptide chains for treatment of growth hormone deficiency, Larode Ltd - EMA/OD/074/13
[Co-ordinators: V. Tillmann / S. Aarum]

The Committee agreed that the condition, growth hormone deficiency, 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 growth hormone modified by fusion with two hydrophilic polypeptide chains was considered justified based on preliminary clinical data showing normalization of IGF-I levels in treated patients.

The condition is chronically debilitating and life-threatening due to cardiovascular risk, decreased bone mass and fractures. The condition was estimated to be affecting approximately 4 in 10,000 people in the European Union, at the time the application was made. This was based on information from literature data.

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 growth hormone modified by fusion with two hydrophilic polypeptide chains may be of significant benefit to those affected by the condition. The sponsor has provided preclinical and clinical data that demonstrate that the product has improved pharmacokinetic properties that may allow for a significantly less frequent administration and therefore improved compliance and better treatment outcome compared to the currently authorised products. The Committee considered that this constitutes a major contribution to patient care.

A positive opinion for recombinant human growth hormone modified by fusion with two hydrophilic polypeptide chains, for treatment of growth hormone deficiency, was adopted by consensus.

2.2.15 Product for the treatment of plasma cell myeloma - EMA/OD/072/13
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for treatment of plasma cell myeloma, the sponsor should further elaborate on:

- the detailed results obtained in vitro showing synergistic/additive effects to other medicinal products with regards to plasma cell apoptosis;

- the details of the preclinical model used for the treatment of plasma cell myeloma, and the results from this study;

- the so far available data form the ongoing phase 1/2 dose escalation clinical study, in patients with plasma cell myeloma.

- Justification of significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preclinical study claiming a possible synergy in addition to other medicinal products.

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

It is well known that extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is also mandatory to justify the safety claims.

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 September meeting.

2.2.16 Sacrosidase for treatment of congenital sucrase-isomaltase deficiency, QOL Therapeutics EU Ltd - EMA/OD/083/13
[Co-ordinators: V. Tillmann / S. Mariz]

The Committee agreed that the condition, congenital sucrase-isomaltase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing sacrosidase was considered justified based on clinical data where the sponsor's product was used in patients with the condition which showed that breath hydrogen excretion a relevant endpoint showed a clinically significant reduction.

The condition is chronically debilitating due to a failure to thrive and fall below expected growth curves. It has also been shown to cause nephrocalcinosis, renal calculi, metabolic acidosis, and hypercalcaemia. The condition was estimated to be affecting 2 in 10,000 people in the European Union, at the time the application was made; this was based on a 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 sacrosidase, for treatment of congenital sucrase-isomaltase deficiency, was adopted by consensus.

2.2.17 for the treatment of parathyroid carcinoma EMA/OD/080/13
[Co-ordinators: B. Dembowska-Bagińska / S. Aarum]

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 in the treatment of parathyroid carcinoma, the sponsor should clarify the following issues:

- the composition of the product in particular certain components where there are known safety concerns ,and

- the activity of the specific products' constituents in parathyroid carcinoma;

- Freund's adjuvant is a toxic compound and described to cause at least severe local reactions. The sponsor should clarify the possible activity of Freund's adjuvant. The information provided with regards to the 15 treated patients should be elaborated. The sponsor is asked to provide more details of the patients (such as a compassionate use program report) clarifying the medical history and clinical evaluation especially with regards to the other treatments (e.g. calcimimetics), tumour and antibody responses, taking into account any possible bias that may have affected the results;

- to provide more details of the reliability of the method used to evaluate tumour responses.to discuss the reliability of the measured endpoints in patients with parathyroid carcinoma administered with the 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 capability of the product to treat hypercalcemia and to elaborate on the information from the compassionate use program to justify the assumption of significant benefit over authorised products for the proposed orphan indication.

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 September meeting.

2.3. Evaluation on-going

The Committee noted that evaluation procedure will commence on 12 July 2013.

2.4. Validation on-going

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

3. Requests for protocol assistance

3.1 Treatment of systemic sclerosis

The Committee was briefed on the significant benefit issues. The protocol assistance letter was adopted.

3.2 Treatment of acromegaly

The Committee was briefed on the significant benefit issues. Final COMP advice to be adopted at the next meeting.

3.3 Treatment of anaplastic thyroid cancer

The Committee was briefed on the significant benefit issues. Final COMP advice to be adopted at the next meeting.

3.4 Treatment of mercury toxicity

The Committee was briefed on the significant benefit issues. Final COMP advice to be adopted at the next meeting.

3.5 Treatment of treatment of primary myelofibrosis

The Committee was briefed on the significant benefit issues. Further issues were raised. Clarifications are needed with regards to significant benefit issues.

4. Overview of applications

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

COMP co-ordinators were appointed for 3 applications submitted and 19 upcoming applications. Two experts were nominated for on-going 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 Procysbi (former name: cysteamine bitartrate) [Cysteamine bitartrate (gastroresistant)] for treatment of cystinosis; Raptor Pharmaceuticals Europe B.V. (EU/3/10/778) [Co-ordinators: V. Saano / S. Mariz]

The COMP concluded that:

The proposed therapeutic indication "Treatment of proven nephropathic cystinosis. Cysteamine reduces cystine accumulation in some cells (e.g. leukocytes, muscle and liver cells) of nephropathic cystinosis patients and, when treatment is started early, it delays the development of renal failure" falls entirely within the scope of the orphan indication of the designated orphan medicinal product orphan indication.

The prevalence of cystinosis was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria and was calculated to be approximately 0.1 in 10,000 at the time of the review of the criteria. The condition is life-threatening and chronically debilitating due to the development of renal failure.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Procysbi may be of significant benefit to those affected by the orphan condition still holds. This is based on the development of a novel formulation that allows for a twice daily administration versus four times daily with the reference product. The Committee considered that this constitutes a major contribution to patient care.

An opinion not recommending the removal of Procysbi [Cysteamine bitartrate (gastroresistant)] (EU/3/10/778) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion (EMA/COMP/415414/2013) was adopted for publication on the EMA website.

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

5.2.1 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]

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

- Justification of significant benefit

The sponsor is requested to further discuss the arguments and data provided for the justification of significant benefit versus vandetanib.

In its written response, and during an oral explanation before the Committee on 10 July, the sponsor provided an indirect comparative discussion of the clinical efficacy of the product versus the authorised vandetanib. In addition, the sponsor argued a lack of significant cardiac toxicity with the product, and argued on the effects of the product in patients previously treated with vandetanib or in patients who were RET mutation negative.

Discussion and COMP opinion is postponed until update on progress of MA procedure.

5.2.2 Defitelio (Defibrotide); Gentium S.p.A. [Co-ordinators: J. Torrent-Farnell / S. Mariz]

a) prevention of hepatic veno-occlusive disease (EU/3/04/211)
b) treatment of hepatic veno-occlusive disease (EU/3/04/212)

Discussion is postponed until update on progress of Ma procedure.

5.2.3 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) [Co-ordinators: V. Stoyanova / L. Fregonese]

Discussion is postponed until update on progress of MA procedure.

5.2.4 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 is postponed until update on progress of 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 is postponed until update on progress of MA procedure.

5.2.6 Scenesse ([Nle4, D-Phe7]-alfa-melanocyte stimulating hormone, Afamelanotide) for treatment of erythropoietic protoporphyria; Clinuvel (UK) Limited (EU/3/08/541) [Co-ordinators: L. Gramstad / S. Mariz]

Discussion is postponed until update on progress of MA procedure.

5.2.7 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 is postponed until update on progress of 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 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)

5.3.3 Gazyva (Obinutuzumab) for treatment of chronic lymphocytic leukemia; Roche Registration (EU/3/12/1054)

5.3.4 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)

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

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

5.3.7 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)

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

5.3.9 Opsumit (Macitentan) for treatment of pulmonary arterial hypertension; Actelion Registration Ltd. (EU/3/11/909)

5.3.10 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)

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

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

5.3.13 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)

5.3.14 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).

5.4. COMP opinion adopted via written procedure following previous meeting

5.4.1 Pheburane (Sodium phenylbutyrate); Lucane Pharma, [Co-ordinators: K. Westermark / S. Aarum]

a) treatment of citrullinaemia type 1 (EU/3/12/949)
b) treatment of ornithine transcarbamylase deficiency (EU/3/12/950)
c) treatment carbamoyl-phosphate synthase-1 deficiency (EU/3/12/951)

The COMP was informed that the negative opinion on the maintenance of criteria for orphan designation for the above mentioned applications has been formally adopted by written procedure on 1 July 2013.

6. Procedural aspects

6.1 Proposals for improvement of the COMP procedures

This topic was postponed for the next meeting.

7. Any other business

7.1 Projects on adaptive licensing

This topic was postponed for the next meeting.

7.2 Informal COMP meeting to be held on 7 November 2013 (at the EMA) following the 150th COMP meeting on 5-6 November 2013

The Committee was informed of the upcoming 150th COMP meeting on 5-6 November 2013.

7.3 Update on international collaboration activities (i.e. FDA and PMDA/MHLW teleconferences)

The Committee was reminded that invitations to participate in the EMA-FDA monthly teleconference have been circulated to the members, and that minutes from teleconference have also been circulated.

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

This topic was postponed for the next meeting.

7.5 Results on the survey on orphan medicinal products development

This topic was postponed for the next meeting.

7.6 Workshop with the PDCO on a definition of conditions for haematological malignancies

This topic was postponed for the next meeting.

7.7 Grounds of major contribution to patient care

This topic was postponed for the next meeting.

7.8 Similarity group

This topic was postponed for the next meeting.

7.9 Scientific Coordination Board

This topic was postponed for the next meeting.

7.10 Judgment of the General Court on Orphacol

Jordi Llinares updated the committee with regards to the judgment of the General Court on Orphacol.

Date of next COMP meeting: 3 - 4 September 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	Бългàрия
Kateřina Kubáčková	Česká Republika
Vacant	Danmark
Frauke Naumann-Winter	Deutschland
Geraldine O'Dea	Éire/Ireland
Josep Torrent Farnell	España
Adriana Andric	Hrvatska
Armando Magrelli	Italia
Ioannis Kkolos	Κύπρος
Dainis Krievins	Latvija (present on the 1st day only)
Aušra Matulevičienė	Lietuva
Henri Metz	Luxembourg
Judit Eggenhofer	Magyarország
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
Vacant	Slovensko
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	CHMP Representative
Vacant	EMA Representative
Vacant	EMA Representative

Observers:

Maria Mavris	Eurordis (present on 1st and 2nd day only)

European Commission:

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

EMA:

Jordi Llinares Garcia	Head of Orphan Medicines
Laura Fregonese	Scientific Administrator
Segundo Mariz	Scientific Administrator (present on 2nd and 3rd day only)
Stylianos Tsigkos	Scientific Administrator
Federica Castellani	Scientific Administrator (for 5.1.1)
Agnieszka Wilk-Kachlicka	Assistant
Frederique Dubois	Assistant

Apologies

Members:

Annie Lorence	France
Sigurdur B. Thorsteinsson	Iceland
Nikolaos Sypsas	Ελλάδα

Observers:

Antonio Blazquez	Agencia Española de Medicamentos y Productos Sanitarios