9 July 2013
EMA/COMP/302197/2013 Rev.1
Human Medicines Development and Evaluation

Committee for Orphan Medicinal Products (COMP)

Minutes of the 11 - 13 June 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).

Contents

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

New members/observers:

- F. Naumann-Winter, representing Germany

- A. Andric, representing Croatia as an observer at the current meeting and as a member from 1 July 2013.

1.1 Adoption of the agenda, EMA/COMP/302134/2013

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting held on 14 - 15 May 2013, EMA/COMP/248636/2013

The minutes were adopted with minor corrections to points 2.2.10, 2.2.13 and 2.2.14.

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 sponsors who have submitted dossier to be considered for orphan designation at the current meeting (2.1.5, 2.2.7). 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[1]

2.1. For opinion

2.1.1 For treatment of narcolepsy - EMA/OD/029/13
[Co-ordinators: L. Gramstad / 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 prevalence issue.

The estimated prevalence by the sponsor was close to the 5/10,000 threshold. Since the absence of cataplexy requires polysomnography for proper narcolepsy diagnosis, this subgroup is often omitted in the reported data, even though this subgroup accounts for about 30% of narcolepsy patients. It was also noted that much of the reported incidence/prevalence data were published about 10-20 years ago or more. The age of the data is even more important if it is considered that in more recent years there has been an increasing interest in sleep disturbances as well as developments of sleep clinics, this

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

could affect the prevalence estimate of the condition and should be taken into account for the calculations.

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

The sponsor withdrew the application on 4 June 2013 prior to responding to the list of questions.

2.1.2 For prevention of graft versus host disease - EMA/OD/026/13

[Co-ordinators: D. Meyer (until 16 May) / 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 the proposed product for prevention of graft-versus-host disease, the sponsor was asked to further elaborate on:

- ✓ the implications and possible consequences related to the cellular components of the product;
- ✓ the sponsor is also invited to better clarify the methodology and results of the clinical study on 13 subjects including e.g. additional treatments administered to the patients of the study in the event of acute GvHD;
- ✓ development of the product.

The sponsor is invited to further discuss:

- ✓ the methodology used to define the cell state as “early” apoptotic besides staining with Annexin V.

In the written response, and during an oral explanation before the Committee on 11 June 2013, the sponsor further elaborated on the issues raised, discussed the components of the proposed product and in particular defined the concept of “early apoptotic state”. The Committee was of the opinion that the data presented, were inconclusive taking into account the remaining uncertainty on the definition of the active component of this product. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 11 June 2013, prior to final opinion.

2.1.3 Autologous bone marrow-derived mesenchymal stromal cells secreting neurotrophic factors for treatment of amyotrophic lateral sclerosis, Brainstorm Cell Therapeutics UK Ltd - EMA/OD/011/13

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

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

- Medical plausibility

With reference to the mechanism of action of the product, and in particular after transplantation of the cells used, the sponsor proposes that the neurotrophic factors will be transported back to the nuclear

area of the neurons. These assumptions are based on published literature about retrograde transport of molecules along axons. However both for anterograde and for retrograde transport an intact microtubule system of the cells is required and therefore it is questioned if this mechanism will be effective in the case of damaged neurons as in ALS.

Most of the data on medical plausibility refers to the general effect of neurotrophic factors in neuroprotection. The sponsor was invited to:

- ✓ discuss data of the cell survival and function after injection, as well as production of NTF;
- ✓ elaborate on the role of the transplantation of the cells used, in the ALS situation and its translation into clinically meaningful effects.

- Justification of significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the on-going Phase I/II study to justify the assumption of significant benefit over riluzole or in combination with it for the proposed orphan indication. Data involving compassionate use patients should be further elaborated.

In the written response, and during an oral explanation before the Committee on 11 June 2013, the sponsor further elaborated on the medical plausibility issue, by discussing in particular in-vivo MRI studies investigating the migration of the product's cells in disease models. The sponsor also further elaborated on the available preliminary clinical data for the justification of significant benefit.

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

The intention to treat the condition with the medicinal product containing autologous bone marrow-derived mesenchymal stromal cells secreting neurotrophic factors was considered justified based on data generated from pre-clinical models and preliminary clinical data in patients with the condition.

The condition is life-threatening and chronically debilitating due to degeneration of the upper and lower motor neurons, leading to progressive weakness of the limb, thoracic and abdominal muscles. Death because of respiratory failure follows on average 2–4 years after symptom onset. The condition was estimated to be affecting 0.7 in 10,000 people in the European Union, at the time the application was made; this was established through 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 autologous bone marrow-derived mesenchymal stromal cells secreting neurotrophic factors may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients with the condition demonstrating a slowing in the progression of some of the symptoms after 6 months of treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous bone marrow-derived mesenchymal stromal cells secreting neurotrophic factors, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.1.4 For treatment of Hunter syndrome (MPSII) - EMA/OD/021/13

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

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

- Justification of significant benefit

The arguments on significant benefit are mainly based on the potentially improved efficacy and safety over the authorised treatment in the condition.

The sponsor was requested to further discuss the molecular and structural features of the applied product that are claimed to justify the clinically relevant advantage of the proposed product over the authorised treatment. In particular, the sponsor was invited to elaborate on how these biologic differences are expected to translate into a clinically relevant advantage. Moreover, the sponsor was asked to provide more details (such as a clinical trial report) of the clinical trial performed and to clarify the clinical results especially with regards to the 6MWT taking into account any possible bias that may have affected the results.

In the written response, and during an oral explanation before the Committee on 11 June 2013, the sponsor elaborated on the structural, physicochemical, immunological and biological features of the proposed product versus the reference product. The sponsor also presented a summary report of a phase I-II single blinded active comparator controlled clinical study in patients affected by the condition.

The Committee considered that the data presented would not justify the assumption of a clinically relevant advantage based on the methodological limitations of the clinical study such as the single-blinded design, and the different baseline patient characteristics between groups.

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

2.1.5 For treatment of renal cell carcinoma - EMA/OD/030/13

[Co-ordinators: B. Bloechl-Daum / S. Tsigkos]

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of renal cell carcinoma, the sponsor was asked to further elaborate on the reported phase I-II study. The design, population, previous treatments in detail and results should be discussed.

- Prevalence

With reference to the published minutes of the COMP plenary meeting of July 2012 (EMA EMA/COMP/404711/2012 Rev.1), “the Committee pointed out that as per the published results of the RARECARE project, the complete prevalence for RCC was 6,718 per 10,000 people. Thus, the Committee was not convinced that the prevalence of the condition remained below the threshold provisioned in the orphan regulation”.

The sponsor was asked to further justify:

- ✓ the inclusion/choice of the sources selected for the estimation of the prevalence of the condition;
- ✓ the exclusion of Rarecare data;
- ✓ the choice of the 5-year partial prevalence adjusted by age and gender as a valid epidemiological index for the purpose of orphan designation.

The sponsor was asked also provide further data with regards to:

- ✓ a ***currently applicable incidence*** of the condition in the EU at the time the application is made, and discuss how this impacts on the prevalence of the condition;
- ✓ an ***updated duration*** of the condition in the EU in light of the currently available authorised products for the condition is question, and discuss how this impacts on the prevalence of the condition in 2013;
- ✓ a ***recalculation of the prevalence*** of the condition taking into consideration the updated incidence and duration, including a ***sensitivity analysis***.

- Significant benefit

As also requested for the purpose of establishing medical plausibility, the sponsor was asked to further elaborate on the reported phase I-II study. The design, population, previous treatments in detail and results should be discussed.

The sponsor withdrew the application on 7 June, prior to the oral explanation.

2.1.6 For treatment of lymphoblastic lymphoma - EMA/OD/027/13

[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:

- Indication

The sponsor was invited to apply for a) treatment of B lymphoblastic leukaemia/lymphoma, and b) treatment of T lymphoblastic leukaemia/lymphoma, in line with the 2008 WHO classification of tumours of haematopoietic and lymphoid tissues.

- Prevalence

In case of an amended indication(s) the sponsor should provide recalculated prevalence figures.

- Significant benefit

The sponsor is arguing significant benefit on two points, the first being reduced risk of causing hypersensitivity and the second being increased availability in case of a shortage of supply of authorised medicines.

The sponsor was invited to:

a) document the relative safety issues of other similar products and substantiate the claim of improved safety of the current product based on data

b) document any serious lack of supply of authorised products in Europe for patients affected by the condition by providing data.

c) position the product in the treatment of T-ALL/LBL and B-ALL/LBL

d) discuss the significant benefit against all authorised products for the condition without limiting the discussion to asparaginase.

In the written response, and during an oral explanation before the Committee on 12 June 2013, the sponsor agreed on amending the indication and provided a cumulative sum for both T-ALL/LBL and B-ALL/LBL, of less than 1.5/10,000. Regarding the significant benefit, the sponsor argued that there is the potential of reduced immunogenicity but did not provide data to support this assumption and concluded that whether the product is indeed less immunogenic "remains to be established". In addition, the documentation of any supply shortages of the authorised products was not provided.

The Committee considered that without any data to justify the improved safety over authorised counterparts and/or data documenting an existing supply shortage for authorised products the significant benefit criterion may not be considered met.In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 June 2013, prior to final opinion.

2.1.7 For treatment of renal cell carcinoma in patients with remaining primary tumour or presence of at least one metastasis - EMA/OD/172/12
[Co-ordinators: B. Bloechl-Daum / 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

Renal cell carcinoma in patients with remaining primary tumour or presence of at least one metastasis should be justified as a distinct medical entity or a valid subset for the purpose of orphan designation. Your attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of renal cell carcinoma in patients with remaining primary tumour or presence of at least one metastasis, the sponsor was asked to further elaborate on:

1. the proposed mechanism of action, as it is not supported by data showing elicitation of immune responses as assumed by the sponsor;

2. the absence of data to investigate if any systemic effects are obtained if the product was to be injected outside or near the tumour;

3. the validity of the preclinical model used for the purpose of proof of concept, since breast cancer cells were used;

4. the appropriateness of the product tested in the preclinical model as a surrogate for the product proposed for designation;

5. the absence of any data with the proposed product in the specific condition as applied for designation. Any available data from the on-going preliminary clinical studies should be included and discussed.

- Prevalence

The sponsor was asked to justify the epidemiological index used, and provide a sensitivity analysis of the assumptions used for the calculation of prevalence.

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential for improved efficacy in the condition. The sponsor was requested to further discuss the arguments provided for significant benefit by positioning the product in the management of the condition versus authorised treatments.

The sponsor was also requested topresent any data to justify the claims for significant benefit in either preclinical or preliminary clinical settings pertaining to the condition as applied for.

In the written response, and during an oral explanation before the Committee on 12 June 2013, the sponsor further discussed the proposed mechanism of action. In particular, histological data from the in vivo study were presented, demonstrating an inflammatory infiltration of the tumour. In addition, pathology specimens from a treated patient from the on-going clinical study were discussed. The proof of concept was also further discussed by some preliminary clinical observations according to which three treated patients exceeded the anticipated survival.

In addition, with regards to the exclusion of effects in the excluded RCC subset, the sponsor referred to another surrogate product. Moreover, prevalence was calculated on the basis of annual number of patients eligible for treatment without justification of the choice of epidemiological index used.

As for the justification of significant benefit, the sponsor discussed the known adverse effects of an authorised product, and there was no comparative discussion as requested by the COMP.

The COMP considered that there is an absence of data from a renal cell carcinoma preclinical model and that the preliminary clinical observations are of uncontrolled nature and may be subject to statistical variation. With regards to the exclusion of a subset of renal cell carcinoma patients, the justifications provided pertained to another product or another condition, which would prevent extrapolation of the observations for the current application. Moreover, with regards to the prevalence issue, the whole RCC population should have been taken into account, since some effects might be also expected in non-surgically treated patients that present with the diagnosis of RCC. The Committee also considered that in the absence of a comparative discussion of the product versus authorised medicines for the condition the significant benefit may not be considered justified.

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

2.1.8 **Granulocyte macrophage colony stimulating factor** for treatment of pulmonary alveolar proteinosis, Serendex ApS - EMA/OD/106/12

[Co-ordinators: V. Saano / 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 the proposed product for treatment of pulmonary alveolar proteinosis, the sponsor was asked to further elaborate on:

- ✓ the mechanism of action of the product in the proposed condition;
- ✓ the bibliographic clinical studies presented to support the medical plausibility. The studies reported by the sponsor are a mixture of safety studies and efficacy studies on different populations and with different endpoints. The sponsor was invited to provide a critical review of the studies containing data on the efficacy of the product, including drawing clear conclusions on the type of data and magnitude of the effects supporting the medical plausibility.

- Justification of significant benefit

The sponsor is invited to discuss the significant benefit of the proposed product in relation to whole lung lavage (WLL).

- Development of the product

The sponsor is invited to clarify on the current state of the product as applied for, including e.g. whether the product to be used is a commercially available GM-CSF or another product. In addition the sponsor was invited to provide some more details on the planned formulation for inhalation and planned studies (clinical and/or preclinical) with the proposed product.

In the written response, and during an oral explanation before the Committee on 12 June 2013, the sponsor further elaborated on the requested issues. Importantly, the sponsor presented additional preliminary clinical data showing a significant reduction in the number of whole lung lavage procedures in a group of patients affected by the condition. This information complemented the review of the existing published studies showing activity of GM-CSF on lung function and lung inflammation in PAP.

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

The intention to treat the condition with the medicinal product containing granulocyte macrophage colony stimulating factor was considered justified based on clinical observational data from the literature showing improvement in functional parameters and blood oxygenation, and reduced need of oxygen supplementation in patients affected by the condition treated with different formulations of the proposed product.

The condition is chronically debilitating mainly due to progressive breathlessness and reduction of lung function leading to the need of oxygen supplementation, and to recurrent infections from opportunistic micro-organisms. The condition was estimated to be affecting less than 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 exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing granulocyte macrophage colony stimulating factor may be of significant benefit to those affected by the condition. The sponsor has provided observational clinical evidence from the literature showing that the treatment with granulocyte macrophage colony stimulating factor can reduce the need of whole lung lavage, currently the only satisfactory method for the treatment of the condition in the European Union. Based on the literature data presented by the sponsor the Committee considered that the possibility of developing the product in the proposed condition constitutes a clinically relevant advantage for the patients affected by pulmonary alveolar proteinosis, particularly in those cases when whole lung lavage is contra-indicated, and for reducing the need of whole lung lavage procedures in patients with recurrent relapses.

A positive opinion for granulocyte macrophage colony stimulating factor, for treatment of pulmonary alveolar proteinosis, was adopted by consensus.

2.1.9 Moxetumomab pasudotox for treatment of acute lymphoblastic leukaemia, MedImmune Ltd - EMA/OD/024/13
[Co-ordinators: B. Dembowska-Bagińska / L. Fregonese]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The Committee considered that hat the condition originally proposed by the sponsor should be renamed as "B-lymphoblastic leukaemia/lymphoma" according to the 2008 WHO classification of haematological tumours of the haematopoietic and lymphoid tumours.

The sponsor was therefore invited to provide an estimate of the prevalence of B-lymphocytic leukaemia/lymphoma.

In the written response the sponsor provided an amended prevalence calculation as requested by the Committee.

The Committee agreed that the condition, B-lymphoblastic leukaemia/lymphoma, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing moxetumomab pasudotox was considered justified based on pre-clinical studies showing selective inhibition of the growth of leukemic cell lines expressing CD22, the main target of the product which, after binding on the cell surface of B cells induces cell death through the cytotoxic activity of the conjugated toxin. In addition the plausibility is supported by the demonstration of tumour regression and cure in models of disseminated leukaemia and by early clinical data on patients not responding to previous treatment.

The condition is chronically debilitating and life-threatening depending on the response to treatment, with acute leukemic forms being fatal in a few weeks if left untreated. The main manifestations of the disease such as persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain, are linked to invasion by the tumour cells of the bloodstream, the bone marrow and/or the lymph nodes and other lymphatic organs, resulting in lack of normal blood cells, bone marrow failure, and specific organ damage. 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 moxetumomab pasudotox may be of significant benefit to those affected by the condition. The selectivity for B cells, due to the restricted expression of CD22 on B cells, offers the potential to eliminate only the cells responsible for the leukaemia while sparing normal cells of the immune system. The preliminary clinical data presented by the sponsor showed favourable responses in B-cell acute lymphoblastic leukaemia patients pre-treated with several different antineoplastic regimens. The above indicates the possibility to use the product in forms of the condition that are resistant and/or relapsing to currently authorised treatments and to direct the treatment specifically to B-cells. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by B-lymphoblastic leukaemia/lymphoma.

A positive opinion for moxetumomab pasudotox, for treatment of B-lymphoblastic leukaemia/lymphoma, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1 (1-methyl-2-nitro-1H-imidazole-5-yl)methyl N,N'-bis(2-bromoethyl)diamidophosphate for treatment of pancreatic cancer, Merck KGaA - EMA/OD/037/13

[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 (1-methyl-2-nitro-1H-imidazole-5-yl)methyl N,N'-bis(2-bromoethyl)diamidophosphate was considered justified based on valid in vivo non-clinical xenograft models as well as preliminary clinical data in patients with advanced pancreatic cancers.

The condition is life-threatening due to a 5 year survival rate of 6% for all forms of the condition. 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 an extensive 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 (1-methyl-2-nitro-1H-imidazole-5-yl)methyl N,N'-bis(2-bromoethyl) diamidophosphate may be of significant benefit to those affected by the condition. The sponsor has provided non-clinical and preliminary clinical data that demonstrate that the product has tumour controlling effects in the non-clinical valid xenograft models when used on its own or in combination with gemcitabine and an improved progression free survival in patients with advanced pancreatic cancer when used in combination with gemcitabine vs patients receiving gemcitabine alone. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (1-methyl-2-nitro-1H-imidazole-5-yl)methyl N,N'-bis(2-bromoethyl)diamidophosphate, for treatment of pancreatic cancer, was adopted by consensus.

2.2.2 *(S)*-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one for treatment of follicular lymphoma, Voisin Consulting S.A.R.L. - EMA/OD/047/13

[Co-ordinators: K. Kubáčková / S. Mariz]

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

The intention to treat the condition with the medicinal product containing *(S)*-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one was considered justified based on preliminary clinical data in patients with advanced follicular lymphoma.

The condition is life-threatening due to a median survival of approximately 8 to 10 years following diagnosis. The condition was estimated to be affecting 3.6 in 10,000 people in the European Union, at the time the application was made; this was based on data obtained from the Globocan 2008 study.

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 *(S)*-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data in patients with advanced follicular lymphoma that demonstrate that their product induced

complete and partial responses. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for *(S)*-3-(1-(9H-purin-6-ylamino)ethyl)-8-chloro-2-phenylisoquinolin-1(2H)-one, for treatment of follicular lymphoma, was adopted by consensus.

2.2.3 For treatment of small cell lung cancer - EMA/OD/040/13

[Co-ordinators: K. Kubáčková / L. Fregonese]

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

- Medical plausibility

Pre-clinical

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

- discuss the plausibility and clinical relevance of studying the combination of paclitaxel and the proposed product in preclinical models taking into account that paclitaxel is at present not authorized for the treatment of small cell lung cancer;

- integrate the pre-clinical data on xenograft models of SCLC with the results of the proposed product and paclitaxel as monotherapy. This is needed in order to evaluate the effects of the proposed product when used in monotherapy in preclinical models and the magnitude of the effects resulting from the combination of the proposed product and paclitaxel.

- discuss the results of the proposed product and paclitaxel as monotherapy and in combination in relation to the effects in the same pre-clinical models with agents currently authorised for the treatment of small cell lung cancer.

Clinical

To establish correctly if there exists a scientific rationale for the development of the proposed product 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 proposed product as monotherapy in small cell lung cancer, also taking into account that the planned development seems to foresee only studies in combination with paclitaxel.

- 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 or major contribution to patient care for the product as compared to what is already authorised for the treatment of the condition.

When the intended use of the proposed product is as monotherapy, the sponsor is invited to substantiate with data and numbers the statement that “*these data are comparable to historical data … in this setting*”. This is in relation to the proposed product results both in sensitive and in relapsing/resistant small cell lung cancer.

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

- Development of the product

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

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 July meeting.

2.2.4 Allogeneic motor neuron progenitor cells derived from human embryonic stem cells

for treatment of amyotrophic lateral sclerosis, California Stem Cell (UK) Ltd - EMA/OD/044/13
[Co-ordinators: V. Stoyanova / S. Mariz]

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

The intention to treat the condition with the medicinal product containing allogeneic motor neuron progenitor cells derived from human embryonic stem cells was considered justified based on results obtained in valid non-clinical in vivo models.

The condition is life-threatening due to a median survival time from onset to death of 39 months. The condition was estimated to be affecting 0.5 in 10,000 people in the European Union, at the time the application was made; this was 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 allogeneic motor neuron progenitor cells derived from human embryonic stem cells may be of significant benefit to those affected by the condition. The sponsor has provided valid preclinical data that demonstrate that the proposed new mode of action is effective and would support the possibility of using this product alone or in combination with riluzole. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic motor neuron progenitor cells derived from human embryonic stem cells, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.5 For prevention of rejection of solid organ transplantation - EMA/OD/043/13

[Co-ordinators: K. Westermark / L. Fregonese]

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

- 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 the proposed product 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 for the development of the product in the proposed condition (rejection of solid organ transplantation);

- the rationale and evidence for extrapolating to the proposed condition rejection of solid orphan transplantation of the data from the study of Di Ianni *et al*. and Brunstein *et al*. on graft versus host disease after bone marrow transplantation.

- Justification of significant benefit

The sponsor should 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.

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 July meeting.

2.2.6 **Belinostat** for treatment of malignant thymomas, TopoTarget A/S - EMA/OD/036/13

[Co-ordinators: B. Dembowska-Bagińska / S. Mariz]

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

The intention to treat the condition with the medicinal product containing belinostat was considered justified based on preliminary clinical data in patients with the relapsed or refractory malignant thymoma where an increase in the progression free survival was noted.

The condition is life-threatening due to a median overall survival time ranging from 19 to 46 months from diagnosis. The condition was estimated to be affecting 0.25 in 10,000 people in the European Union, at the time the application was made; this was established through a literature search and a German Cancer Registry.

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 belinostat, for treatment of malignant thymomas, was adopted by consensus.

2.2.7 **Daratumumab** for treatment of multiple myeloma, Janssen-Cilag International N.V. - EMA/OD/038/13

[Co-ordinators: M. Možina / S. Tsigkos]

Following review of the application by the Committee, it was agreed to rename the condition to “plasma cell myeloma”, in line with the WHO classification of tumours of haematopoietic and lymphoid tissues

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

The intention treat the condition with the medicinal product containing daratumumab was considered justified based on preliminary clinical studies showing responses in previously relapsed or refractory patients, treated with the product.

The condition is life-threatening due to the development of hypercalcaemia, renal insufficiency, anaemia and bone lesions, and life-threatening with an overall survival of up to approximately 45 months for newly diagnosed patients. The condition was estimated to be affecting approximately 1.75 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 daratumumab may be of significant benefit to those affected by the condition. The sponsor has submitted preliminary clinical data in relapsed or refractory plasma cell, myeloma patients; of the 12 patients treated in the higher dose cohorts, 5 partial responses according to the International Myeloma Working Group criteria have been reported. In addition, a prolongation of progression free survival is reported compared to the lower doses cohorts. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for daratumumab, for treatment of plasma cell myeloma, was adopted by consensus.

2.2.8 Dexamethasone sodium phosphate for encapsulation in human autologous erythrocytes

Dexamethasone sodium phosphate for encapsulation in human autologous erythrocytes for treatment of Ataxia Telangiectasia, Erydel S.p.A. - EMA/OD/052/13
[Co-ordinators: A. Lorence / S. Mariz]

The Committee considered that the name of the active substance should be changed to “dexamethasone sodium phosphate encapsulated in human autologous erythrocytes”.

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

The intention to treat the condition with the medicinal product containing dexamethasone sodium phosphate encapsulated in human autologous erythrocytes was considered justified based on preliminary clinical data in patients with the condition.

The condition is life-threatening and chronically debilitating due to the progressive destruction of the motor control area of the brain leading to a lack of balance and coordination as well as affecting the immune system which is associated with infections and an increased risk of leukaemia and lymphoma. The condition was estimated to be affecting 0.1 in 10,000 people in the European Union, at the time the application was made; this is based on personal communications from specialised centres for ataxia telangiectasia.

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 dexamethasone sodium phosphate encapsulated in human autologous erythrocytes, for treatment of ataxia telangiectasia, was adopted by consensus.

2.2.9 For prevention of recurrent hepatitis C virus induced liver disease in liver transplant recipients - EMA/OD/050/13
[Co-ordinators: N. Sypsas / S. Tsigkos]

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

- Proposed indication

The sponsor should 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 the development of the proposed product for prevention of recurrent hepatitis C in liver transplant recipients, the sponsor should 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 available preliminary clinical data 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 should justify the inclusion/choice of the sources selected for the estimation of the prevalence of the condition. The sponsor should describe and justify the methodology used for the prevalence calculation.

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

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 July meeting.

2.2.10 For treatment of snakebite envenomation - EMA/OD/068/13
[Co-ordinators: I. Kkolos / 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 of the proposed product for treatment of snakebite envenomation, the sponsor is invited to present data (e.g. from literature) regarding the efficacy of the proposed product in snakebite envenomation. In case the sponsor aims at presenting data using otherproducts , extrapolation of the data to the proposed product should be discussed and justified.

The sponsor is 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 is 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 is invited to discuss the clinical relevance of the results of the neutralization assay to an assumed in vivo clinical added value of the product as compared to what already authorized in the EU for the treatment of the condition.

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

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 July meeting.

2.2.11 Ex-vivo expanded autologous human corneal epithelium containing stem cells for treatment of limbal stem cell deficiency, University Newcastle upon Tyne - EMA/OD/065/13
[Co-ordinators: V. Stoyanova / S. Mariz]

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

The intention to treat the condition with the medicinal product containing ex-vivo expanded autologous human corneal epithelium containing stem cells was considered justified based on preliminary clinical data in patients affected by the condition.

The condition is chronically debilitating due to discomfort and reduced or complete loss of vision. 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 ex-vivo expanded autologous human corneal epithelium containing stem cells, for treatment of limbal stem cell deficiency, was adopted by consensus.

2.2.12 Fosbretabulin tromethamine for treatment of ovarian cancer, Diamond BioPharm Limited - EMA/OD/039/13
[Co-ordinators: K. Kubáčková / S. Mariz]

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

The intention to treat the condition with the medicinal product containing fosbretabulin tromethamine was considered justified based on preliminary clinical data inpatients with the condition.

The condition is life-threatening due to a reduced life-expectancy at 5 years. 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 established based on data from the Globocan 2008 study.

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 fosbretabulin tromethamine may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that fosbretabulin tromethamine when used in combination with carboplatin and paclitaxel in patients with platinum resistant ovarian cancers provided a favourable partial response as established with the RESIST and CA-125 criteria. The Committee considered that this constitutes a clinically relevant advantage

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

2.2.13 Heterologous Human Adult Liver-derived Progenitor cells for treatment of hyperargininaemia, Promethera Biosciences - EMA/OD/060/13
[Co-ordinators: K. Westermark / S. Aarum]

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

The intention to treat the condition with the medicinal product containing heterologous human adult liver-derived progenitor cells was considered justified based on preclinical results.

The condition is chronically debilitating due to the consequences of metabolic decompensation that leads to developmental delay, mental disability, and other types of neurological damage. The life threatening nature is justified by the overall increased mortality rate associated with the condition. The condition was estimated to be affecting approximately 0.02 in 10,000 people in the European Union, at the time the application was made.

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

A positive opinion for heterologous human adult liver-derived progenitor cells, for treatment of hyperargininaemia, was adopted by consensus.

2.2.14 Heterologous Human Adult Liver-derived Progenitor cells for treatment of carbamoylphosphate synthetase I deficiency, Promethera Biosciences - EMA/OD/057/13
[Co-ordinators: K. Westermark / S. Aarum]

Following review of the application by the Committee, it was agreed to rename the condition to “carbamoyl-phosphate synthase-1 deficiency”.

The Committee agreed that the condition, carbamoyl-phosphate synthase-1 deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing heterologous human adult liver-derived progenitor cells was considered justified based on preclinical results.

The condition is chronically debilitating due to the consequences of metabolic decompensation that leads to developmental delay, mental disability, and other types of neurological damage. The life threatening nature is justified by the overall increased mortality rate associated with the condition. The condition was estimated to be affecting in the range of 0.04-0.05 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 heterologous human adult liver-derived progenitor cells may be of significant benefit to those affected by the condition.

The sponsor has provided preclinical data suggesting that when the product is engrafted, it differentiates into functional hepatic cells. Therefore, the product is expected to decrease acute hyperammonaemia crises and improve the metabolic control of the patients.

A positive opinion for heterologous human adult liver-derived progenitor cells, for treatment of carbamoyl-phosphate synthase-1 deficiency, was adopted by consensus.

2.2.15 Heterologous Human Adult Liver-derived Progenitor cells for treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome), Promethera Biosciences - EMA/OD/063/13
[Co-ordinators: K. Westermark / S. Aarum]

The Committee agreed that the condition, ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing heterologous human adult liver-derived progenitor cells was considered justified based on preclinical results.

The condition is chronically debilitating due to the consequences of metabolic decompensation that leads to developmental delay, mental disability, and other types of neurological damage. The life threatening nature is justified by the overall increased mortality rate associated with the condition. The condition was estimated to be affecting less than 0.01 in 10,000 people in the European Union, at the time the application was made.

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

A positive opinion for heterologous human adult liver-derived progenitor cells, for treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome), was adopted by consensus.

2.2.16 Heterologous Human Adult Liver-derived Progenitor cells for treatment of citrullinaemia type 2, Promethera Biosciences - EMA/OD/062/13
[Co-ordinators: K. Westermark / S. Aarum]

The Committee agreed that the condition, type 2, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing heterologous human adult liver-derived progenitor cells was considered justified based on preclinical results.

The condition is chronically debilitating due to the consequences of metabolic decompensation that leads to developmental delay, mental disability, and other types of neurological damage. The life threatening nature is justified by the overall increased mortality rate associated with the condition. The condition was estimated to be affecting in the range of 0.01-0.09 in 10,000 people in the European Union, at the time the application was made.

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

A positive opinion for heterologous human adult liver-derived progenitor cells, for treatment of citrullinaemia type 2, was adopted by consensus.

2.2.17 Heterologous Human Adult Liver-derived Progenitor cells for treatment of argininosuccinic aciduria, Promethera Biosciences - EMA/OD/059/13
[Co-ordinators: K. Westermark / S. Aarum]

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

The intention to treat the condition with the medicinal product containing heterologous human adult liver-derived progenitor cells was considered justified based on preclinical results.

The condition is chronically debilitating due to the consequences of metabolic decompensation that leads to developmental delay, mental disability, and other types of neurological damage. The life threatening nature is justified by the overall increased mortality rate associated with the condition. The condition was estimated to be affecting approximately 0.19 in 10,000 people in the European Union, at the time the application was made.

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

A positive opinion for heterologous human adult liver-derived progenitor cells, for treatment of argininosuccinic aciduria, was adopted by consensus.

2.2.18 Heterologous Human Adult Liver-derived Progenitor cells for treatment of citrullinaemia type 1, Promethera Biosciences - EMA/OD/058/13
[Co-ordinators: K. Westermark / S. Aarum]

The Committee agreed that the condition, citrullinaemia type 1, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing heterologous human adult liver-derived progenitor cells was considered justified based on preclinical results.

The condition is chronically debilitating due to the consequences of metabolic decompensation that leads to developmental delay, mental disability, and other types of neurological damage. The life threatening nature is justified by the overall increased mortality rate associated with the condition. The condition was estimated to be affecting approximately 0.06 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 heterologous human adult liver-derived progenitor cells may be of significant benefit to those affected by the condition.

The sponsor has provided preclinical data suggesting that when the product is engrafted, it differentiates into functional hepatic cells. Therefore, the product is expected to decrease acute hyperammonaemia crises and improve the metabolic control of the patients.

A positive opinion for heterologous human adult liver-derived progenitor cells, for treatment of citrullinaemia type 1, was adopted by consensus.

2.2.19 Heterologous Human Adult Liver-derived Progenitor cells for treatment of N-acetylglutamate synthetase deficiency, Promethera Biosciences - EMA/OD/061/13
[Co-ordinators: K. Westermark / S. Aarum]

The Committee agreed that the condition, N-acetylglutamate synthetase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing heterologous human adult liver-derived progenitor cells was considered justified based on preclinical results.

The condition is chronically debilitating due to the consequences of metabolic decompensation that leads to developmental delay, mental disability, and other types of neurological damage. The life threatening nature is justified by the overall increased mortality rate associated with the condition. The condition was estimated to be affecting approximately 0.01 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 heterologous human adult liver-derived progenitor cells may be of significant benefit to those affected by the condition.

The sponsor has provided preclinical data suggesting that when the product is engrafted, it differentiates into functional hepatic cells. Therefore, the product is expected to decrease acute hyperammonaemia crises and improve the metabolic control of the patients.

A positive opinion for heterologous human adult liver-derived progenitor cells, for treatment of N-acetylglutamate synthetase deficiency, was adopted by consensus.

2.2.20 Human hemin for prevention of ischaemia reperfusion injury associated with solid organ transplantation, Borders Technology Management Ltd - EMA/OD/018/13
[Co-ordinators: K. Westermark / L. Fregonese]

The Committee agreed that the condition, ischaemia reperfusion injury associated with 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 human hemin was considered justified based on extensive literature showing protective effects of hemin on graft function in different pre-clinical models of solid organ transplantation. The sponsor also presented a clinical

study from the literature demonstrating that a single dose of the product improves reperfusion patterns during ischemia reperfusion injury.

The condition is life-threatening and chronically debilitating due to the possible occurrence of graft failure and of delayed and sub-optimal graft function. The population of patients eligible for prevention of the condition was estimated to be approximately 0.6 in 10,000 people per year 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 human hemin may be of significant benefit to the population at risk of developing the condition. Currently preservation solutions are authorized for the prevention of the condition, and are added to the organ that is being transplanted. Human hemin has a different mechanism of action as compared to preservation solutions and it will be administered to the patients, thereby offering the potential advantage of longer duration of the protective effect. It will be also possible to use human hemin as complementary and add-on prevention to preservation solutions. The sponsor provided pre-clinical and clinical evidence from literature showing that human hemin is able to improve the function of transplanted organs when administered for a few days around the day of transplantation. All the above is considered by the Committee a clinically relevant advantage for the patient population at risk of ischaemia/reperfusion injury associated with solid organ transplantation.

A positive opinion for human hemin, for prevention of ischaemia reperfusion injury associated with solid organ transplantation, was adopted by consensus.

2.2.21 For treatment of chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL) - EMA/OD/056/13
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

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

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

2.2.22 Idelalisib for treatment of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM), Gilead Sciences International Ltd - EMA/OD/055/13
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

Following review of the application by the Committee, it was agreed to rename the condition to "lymphoplasmacytic lymphoma".

The Committee agreed that the condition, lymphoplasmacytic 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 data showing responses in relapsed or refractory patients treated with the product.

The condition is chronically debilitating and life-threatening due to bone marrow dysfunction, lymphadenopathy, splenomegaly and paraproteinaemia resulting in hyperviscosity, autoimmunity, cryoglobulinaemia, coagulopathies and neuropathies. The condition was estimated to be affecting approximately 0.06 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 that show favourable responses in patients who were refractory or relapsed following treatment with available authorised products. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for idelalisib, for treatment of lymphoplasmacytic lymphoma, was adopted by consensus.

2.2.23 For treatment of marginal zone lymphoma - EMA/OD/054/13
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- 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 is invited to apply for the underlying entities separately.

- Seriousness

The sponsor is 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 should recalculate the prevalence estimate based on relevant epidemiological studies and registers.

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

2.2.24 Idelalisib for treatment of follicular lymphoma, Gilead Sciences International Ltd - EMA/OD/053/13
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

The intention to treat the condition with the medicinal product containing idelalisib was considered justified 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 lymphadenopathy, splenomegaly, bone marrow dysfunction and the potential of transformation to aggressive lymphoma. The condition was estimated to be affecting approximately 2.2 in 10,000 people in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing 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 follicular lymphoma, was adopted by consensus.

2.2.25 For treatment of osteosarcoma - EMA/OD/020/13
[Co-ordinators: D. O'Connor / 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 the development of the proposed product for treatment of osteosarcoma, the sponsor should 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 relevant preliminary clinical study, 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 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.

- Justification of significant benefit

The arguments on significant benefit are based on the potential improved efficacy and improved safety in the condition. The sponsor should further elaborate and quantify these arguments, and position the product versus all satisfactory treatments without limiting the discussion to intravenous cisplatin.

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 July meeting.

2.2.26 For treatment of acromegaly - EMA/OD/042/13
[Co-ordinators: K. Westermark / 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 of the proposed product for treatment of acromegaly, the sponsor should further elaborate on:

- the role of the different components of the excipient mix in the junction-opening activity, and to which extent these components contribute to the pharmacodynamic of the product.

- Justification of significant benefit

The sponsor is 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 is 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.

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 July meeting.

2.2.27 For treatment of prurigo nodularis - EMA/OD/046/13
[Co-ordinators: J. Torrent-Farnell / S. Tsigkos]

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

- 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 development of the proposed product for 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 other products 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 as 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 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 July meeting.

2.2.28 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]

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

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

- the possible use of the product with chemotherapeutic agents other than cisplatin;

- the subset 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 of the proposed product for treatment of squamous cell carcinoma of the head and neck, in combination with chemotherapy, the sponsor should further discuss:

- the antineoplastic activity of the product 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 140 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 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 July meeting.

2.2.29 Recombinant human monoclonal antibody against hepatitis B virus for prevention of Hepatitis B Recurrence Following Liver Transplantation, CRO-PharmaNet Services GmbH - EMA/OD/045/13
[Co-ordinators: B. Dembowska-Bagińska / L. Fregonese]

Following review of the application by the Committee, it was agreed to rename the condition to "hepatitis B re-infection following liver transplantation".

The Committee agreed that the condition, hepatitis B re-infection following liver transplantation, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing recombinant human monoclonal antibody against hepatitis B virus was considered justified based on preclinical data showing protection against infection with hepatitis B virus.

The condition is life-threatening and chronically debilitating due to the development of graft disease of variable severity leading to reduced graft survival and graft failure, with need of re-transplantation, or death. The presence of hepatitis B re-infection reduces 3-year survival of transplanted patients from average 89% to 58%.

The population of patients eligible for prevention of the condition was estimated to be less than 0.1 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 recombinant human monoclonal antibody against hepatitis B virus may be of significant benefit to the population at risk of developing the condition. The sponsor has provided preclinical data that demonstrate a broad protection against hepatitis B infection, including against mutant forms that allow the virus to escape the immune response of the patients and the response to the currently authorized immunoglobulin-based products, such as the S escape mutant G145R. The Committee considered that this constitutes a clinically relevant advantage for the population at risk of hepatitis B re-infection following liver transplantation.

A positive opinion for recombinant human monoclonal antibody against hepatitis B virus, for prevention of hepatitis B re-infection following liver transplantation, was adopted by consensus.

2.2.30 For treatment of systemic transthyretin-related amyloidosis - EMA/OD/049/13
[Co-ordinators: K. Westermark / S. Tsigkos]

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

- 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 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 should 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 should 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 is invited to further elaborate on the claims of significant benefit by taking into consideration that:

1) the proposed product is argued to have the same mechanism of action as the authorised counterpart

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

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

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

2.2.31 For treatment of autosomal dominant polycystic kidney disease - EMA/OD/066/13
[Co-ordinators: A. Corrêa Nunes / S. Aarum]

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

- Prevalence

The sponsor has based the prevalence calculation on two publications and the ERA-EDTA registry data. The sponsor should 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 is 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”.

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 July meeting.

2.2.32 For treatment of acute myeloid leukaemia - EMA/OD/064/13
[Co-ordinators: B. Dembowska-Bagińska / S. Mariz]

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

- Justification of significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preclinical xenograft 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.

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

2.3. COMP opinions adopted via written procedure following previous meeting

- **Copper meso-5,15-bis[3-[(1,2-dicarba-closo-dodecaboranyl)methoxy]phenyl]-meso-12,20-dinitroporphyrin** for treatment of squamous cell carcinoma of the head and neck in patients undergoing radiotherapy, MorEx Development Partners LLP - EMA/OD/022/13
- **Immortalised human C3A hepatoblastoma cells** for treatment of acute liver failure, Vital Therapies Limited - EMA/OD/032/13
- **Synthetic double-stranded siRNA oligonucleotide directed against the keratin 6a N171K mutation** for treatment of pachyonychia congenita, Alan Irvine - EMA/OD/028/13

2.4. Evaluation on-going

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

2.5. Validation on-going

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

3. Requests for protocol assistance

3.1 For treatment of systemic sclerosis

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

3.2 Protocol assistance letters adopted via written procedure following previous meeting:

- For treatment of neovascular glaucoma
- For treatment peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated).

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 20 upcoming applications.

4.2 Update on orphan applications for Marketing Authorisation

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

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

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

5.1.1 Pomalidomide Celgene (Pomalidomide) for treatment of multiple myeloma; Celgene Europe Ltd. (EU/3/09/672) [Co-ordinators: K. Kubackova / S. Mariz]

The COMP concluded that:

The proposed therapeutic indication "treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior treatment regimens, including both lenalidomide and bortezomib, and have demonstrated disease progression on the last therapy "falls entirely within the scope of the orphan indication of the designated orphan medicinal product orphan indication.

The prevalence of multiple myeloma was estimated to be 0.5 in 10,000 which remains below 5 in 10,000 at the time of the review of the designation criteria. The condition is chronically debilitating and life-threatening, particularly with regards to the development of osteolytic lesions, renal failure and the cytopenias and its clinical complications such as infections and fatigue.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that pomalidomide may be of potential significant benefit to those affected by the orphan condition still holds as the sponsor has established that there was a significant improvement in progression free survival in patients who had refractory or relapsed and refractory multiple myeloma and who had failed both lenalidomide and bortezomib therapies.

An opinion not recommending the removal of Pomalidomide Celgene (Pomalidomide) (EU/3/09/672) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summary of the COMP opinion (EMA/351975/2013) was adopted for publication on the EMA website.

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

5.2.1 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. Stoynova / L. Fregonese]

Following the initial discussion on the review of the orphan designation a discussion will be held by the COMP in July 2013.

5.2.2 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] [Patient expert: A. Froehlich]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to further support with data and justify the potential significant benefit of

Cysteamine bitartrate (gastroresistant) (Procysbi) over Cystagon for treatment of cystinosis regarding major contribution to patient.

In its written response, and during an oral explanation before the Committee on 11 June, the sponsor argued that it has captured QoL data in its long-term safety extension study and presented a manuscript with the results. The sponsor argued that quality of life improved over 12 months treatment with Procysbi vs. baseline (Cystagon), as measured with the validated PedsQL QoL scale.Following the initial discussion on the review of the orphan designation, the Committee expressed a positive trend on the maintenance of the designation. The committee considered in particular that the development of the new formulation allows for a twice daily administration, versus four times daily administration with the reference product, which was considered to be a major contribution to patient care. The patient expert opinion was also in favour of the maintenance of the orphan status at the time of marketing authorisation. A formal opinion to be adopted by the COMP in July 2013.

5.2.3 Cometriq [Cyclopropane-1,1-dicarboxylic acid [4-(6,7-dimethoxy-quinolin-4-yloxy)-phenyl]-amide (4-fluoro-phenyl)-amide, (L)-malate salt] for treatment of medullary thyroid carcinoma; TMC Pharma Services Ltd (EU/3/08/610) [Co-ordinators: B. Bloechl-Daum / S. Aarum]

The Committee considered that the sponsor should clarify the significant benefit.

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 in July meeting.

5.2.4 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 CHMP 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 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)

5.3.3 Defitelio (Defibrotide); Gentium S.p.A.

- prevention of hepatic veno-occlusive disease (EU/3/04/211)

- treatment of hepatic veno-occlusive disease (EU/3/04/212)

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

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

5.3.6 Holoclar (former name: GPLSCD01) (Ex vivo expanded autologous human corneal epithelium containing stem cells) for treatment of corneal lesions, with associated corneal (limbal) stem cell deficiency, due to ocular burns; Chiesi Farmaceutici S.p.A. (EU/3/08/579)

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

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

5.3.9 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)

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

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

5.3.12 PAS-GR (Para-aminosalicylic acid) for treatment of tuberculosis; Lucane Pharma SA (EU/3/10/826)

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

5.3.14 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)

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

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

5.3.17 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)

5.3.18 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. Appeal procedure

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

Following the COMP recommendation to remove Pheburane, sodium phenylbutyrate (EU/3/12/949) for the treatment of citrullinaemia type 1, from the Community Register of Orphan Medicinal Products, on 5 June 2013, the sponsor submitted detailed grounds for appeal of the COMP opinion of 17 April 2013.

The COMP coordinator for this procedure was Prof K Westermark and the EMA coordinator was Dr S Aarum.

Detailed grounds for appeal submitted by the applicant

The Sponsor presented their details grounds for re-examination in writing on 5 June 2013 and at an oral explanation on 11 June 2013.

The sponsor argued that data are available which demonstrate that Pheburane administration leads to an improvement in measurements of quality of life (QoL).

The sponsor further argued that data and information are also available which demonstrate that the graduated dosing spoon supplied with Pheburane allows accurate and simple measurements of daily dose and dose increments, in contrast to the system available with the marketed product.

The COMP assessed the detailed grounds for appeal and the argumentations presented by the sponsor during the oral explanation.

Overall conclusion on the grounds for appeal

During the review of the criteria for orphan designation at the time of Marketing Authorisation the sponsor presented data from an on-going cohort (Temporary Authorisation for Use; ATU) in France. At the time of the initial opinion, the Committee concluded that the sponsor has shown that there is improved palatability and that there are considerable difficulties with the administration of Ammonaps. However, in view of the Committee, the sponsor did not provide data to confirm that the new proposed formulation would result in improved clinical consequences.

At the time of appeal, the sponsor presented uncontrolled data from observations in patients with different treatment background within the ongoing cohort (ATU) mentioned above.

The COMP concluded the data was inconclusive and presented significant deficiencies that do not allow concluding that Pheburane is of significant benefit for patients.

The sponsor discussed the potential benefit of a more accurate dosing of Pheburane with the proposed dosing device. No data on the dosing accuracy for Pheburane was presented. Therefore, the appeal grounds were not considered to contain valid data to substantiate the significant benefit on the grounds of a clinically relevant advantage or major contribution to patient care in relation to dosing accuracy.

Recommendations following appeal

Based on the assessment of the detailed grounds for appeal and the argumentations presented by the sponsor during the oral explanation, the COMP concluded that:

- the data provided with Pheburane does not justify significant benefit as it has not demonstrated to improve the compliance with the product or the quality of life of patients affected by the condition;
- the appeal grounds do not contain valid data to substantiate the significant benefit on the grounds of a clinically relevant advantage or major contribution to patient care in relation to dosing accuracy;
- therefore, the sponsor has not established that sodium phenylbutyrate is still of significant benefit to those affected by the condition.

Having considered the detailed grounds for appeal submitted by the sponsor and all the supporting data, the COMP re-examined its initial opinion and in its final opinion concluded by consensus, on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are not satisfied.

The COMP recommends that Pheburane (sodium phenylbutyrate) for the indications:

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)

is removed from the Community Register of Orphan Medicinal Products.

Post-meeting note:

The final opinions recommending the removal of Pheburane (sodium phenylbutyrate) (EU/3/12/949, EU/3/12/950, EU/3/12/951) from the EC Register of Orphan Medicinal Products were adopted via written procedure on 1 July 2013.

6. Procedural aspects

6.1 European Medicines Agency Human Scientific Committees' Working Party with Healthcare Professionals' Organisations (HCPWP)

The COMP appointed K. Kubačkova to represent the Committee in the HCPWP.

7. Any other business

7.1 Projects on adaptive licensing

The Committee was briefed on the on-going project. After discussion it was agreed that the comments from the Committee will be summarised in a letter to be forwarded for discussion to the group leading the project.

Date of next COMP meeting: 9 - 11 July 2013

List of participants

Chair:

Bruno Sepodes

Vice-Chair:

Lesley Greene	Volunteer patient representative for Eurordis

COMP Members:

André Lhoir	België/Belgique/Belgien
Irena Bradinova	Бълга̀рия
Kateřina Kubáčková	Česká Republika (present on the 1st day only)
Vacant	Danmark
Frauke Neumann-Winter	Deutschland
Vallo Tillmann	Eesti (present on the 1st and 2nd day only)
Nikolaos Sypsas	Ελλάδα
Josep Torrent Farnell	España
Annie Lorence	France
Sigurdur B. Thorsteinsson	Iceland (present on the 1st and 2nd day only)
Armando Magrelli	Italia
Ioannis Kkolos	Κύπρος
Dainis Krievins	Latvija (present on the 1st and 2nd day only)
Aušra Matulevičienė	Lietuva
Judit Eggenhofer	Magyarország
Albert Vincenti	Malta
Violeta Stoyanova-Beninska	Nederland
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Österreich (present on 2nd day only)
Bożenna Dembowska-Bagińska	Polska
Ana Corrêa-Nunes	Portugal
Flavia Saleh	România
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 (present on the 1st and 2nd day only)
Vacant	EMA Representative
Vacant	EMA Representative

Observers:

Adriana Andrić	Croatia
Maria Mavris	Eurordis

European Commission:

Agnès Mathieu	DG Health and Consumers

EMA:

Jordi Llinares Garcia	Head of Orphan Medicines
Stiina Aarum	Scientific Administrator
Laura Fregonese	Scientific Administrator
Segundo Mariz	Scientific Administrator
Stylianos Tsigkos	Scientific Administrator
Federica Castellani	Scientific Administrator (for 5.1.1)
Agnieszka Wilk-Kachlicka	Assistant
Frederique Dubois	Assistant

Apologies

Members:

Geraldine O'Dea	Éire/Ireland
Henri Metz	Luxembourg

Observers:

Antonio Blazquez	Agencia Española de Medicamentos y Productos Sanitarios