7 November 2012
EMA/COMP/589195/2012
Human Medicines Development and Evaluation

Committee for Orphan Medicinal Products (COMP)

Minutes of the 3 - 5 October 2012 meeting

Note on access to documents

Documents under points 1.1 and 2 to 7 cannot be released at present as they are currently in draft format or are classified as confidential. They will become public when adopted in their final form or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

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1. Introduction

1.1 Adoption of the agenda, EMA/COMP/582562/2012

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the COMP meeting held on 4 - 5 September 2012, EMA/COMP/471400/2012

The minutes were adopted with minor corrections.

1.3 Conflicts of Interest

The COMP secretariat was informed as follows:

- Eurordis receives funding from the sponsors who have submitted dossiers to be considered for orphan designation at the current meeting (2.2.2, 2.2.3, 2.2.5, 2.2.10, 2.2.14 and 2.2.29). Nevertheless, no direct conflicts of interest have been identified for L. Greene and B. Byskov Holm, who are the volunteer patient representatives for EURORDIS.

- EGAN received grants from the sponsor/s for applications under agenda point 2.2.5. 2.2.14 and 5.2.3 (review of the OMP designation). Nevertheless, no direct conflicts of interest have been identified for P. Evers, who is representing EGAN in the COMP.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 For treatment of renal cell carcinoma - EMA/OD/094/12
[Co-ordinators: B. Bloechl-Daum / L. Fregonese]

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

- Prevalence

The sponsor was invited to further discuss the 5-year and complete prevalence of renal cell carcinoma, taking into account recent publications pointing to prevalence higher than 5 in 10,000 such as the published results of the RARECARE project, where the complete prevalence for RCC was 6.7 per 10,000 people.

- Significant benefit

The sponsor was invited to further elaborate on the grounds for significant benefit and in particular on the preclinical studies where the product was used in combination or compared with currently authorized products, and on the available clinical data in renal cell carcinoma.

In the written response, and during an oral explanation before the Committee on 3 October 2012, the sponsor argued with regards to the prevalence, that even though there has been a documented increase in the incidence of the condition in the nineties, there might be stabilization, or even a

[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).

decrease of the incidence thereon. The sponsor argued that this might not be reflected in the RARECARE project, and therefore the prevalence quoted may not be valid. The sponsor argued that based on 5-year prevalence data from Globocan 2008 (giving 5,11 for all kidney cancers in EU27), and assuming that up to 90% of kidney cancers are renal cell carcinoma, the prevalence criterion can be consider met. As regards the significant benefit, the sponsor described the mechanism of action of the proposed product, and stressed that it has multiple targets implicated in the pathophysiology of the proposed condition. The sponsor also discussed preliminary clinical data, and argued a favourable comparison of progression free survival when compared with published data from authorised counterparts.

The Committee considered that the stabilisation or decrease of incidence of the condition in the last decade as proposed by the sponsor was not substantiated by data; furthermore, the duration of the proposed condition had not been analysed and taken into consideration for the calculation of the prevalence estimate. Therefore, the prevalence criterion could not be considered justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 4 October 2012, prior to final opinion.

2.1.2 Allogenic retinal epithelial cells transfected with plasmid vector encoding human ciliary neurotrophic factor for treatment of macular telangiectasia type 2, Enpharma Ltd - EMA/OD/160/11

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

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the product for treatment of macular telangiectasia type 2, the sponsor was invited to further elaborate on:

> - the relevance and applicability of the results obtained with neurotrophic factor 4 in the retina of a model of the proposed condition, and to the proposed product constituted by cells secreting human ciliary neurothropic factor;
>
> - the relevance and applicability of the clinical activity of the product as seen in age-related macular degeneration and retinitis pigmentosa to the proposed condition Macular telangiectasia type 2;
>
> - the availability of any results in models more closely reflecting the proposed condition, and/or any available clinical results in the proposed condition.

In the written response, and during an oral explanation before the Committee on 3 October 2012, the sponsor elaborated on the relevance of the preclinical models. It was stressed that apoptosis of photoreceptor cells is an intrinsic feature of the condition, and that bridging with a surrogate product (human CNTF) in the conditional Muller cell ablation model would allow extrapolations to be made with regards to the medical plausibility. The Committee considered that the proposed model and the surrogate product (human CNTF) would be relevant to draw conclusions for the proposed condition and product as applied for and accepted the medical plausibility.

For the purpose of orphan designation, the COMP considered that the active ingredient should be renamed as "encapsulated human retinal pigment epithelial cell line transfected with plasmid vector expressing human ciliary neurotropic factor".

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

The intention to treat the condition is justified on the basis of data in a preclinical model. In this model, that mimics the features of the proposed condition, administration of human ciliary neurotropic factor has been shown to rescue photoreceptor cells from cell death. Macular telangiectasia type 2 was estimated to be affecting less than 2.3 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to visual impairment. There is, at present, no satisfactory method of treatment that has been authorised in the European Union.

A positive opinion for encapsulated human retinal pigment epithelial cell line transfected with plasmid vector expressing human ciliary neurotropic factor, for treatment of macular telangiectasia type 2, was adopted by consensus.

2.1.3 For treatment of small cell lung cancer - EMA/OD/098/12

[Co-ordinators: D. O'Connor / S. Mariz]

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

- Medical plausibility

The justification of medical plausibility should include a more thorough discussion and presentation of the non-clinical aspects of the application and the available clinical data, with a focus on the claimed indication of small cell lung cancer. To establish if a scientific rationale exists for the development of the medicine for treatment of small cell lung cancer, the sponsor was invited to further elaborate on:

- the relevance of the preclinical model used for the treatment of small cell lung cancer,

- the particulars of the patients, treatments and assessments as regards the preliminary clinical observations presented.

- Justification of significant benefit

No specific non-clinical or clinical evidence has been provided to support the claim of significant benefit. The sponsor was asked to discuss how the medicine is expected to benefit patients in the claimed indication of small cell lung cancer, specifically, what is the clinically relevant advantage vis a vis the authorised treatments.

In addition, the sponsor was asked to further elaborate on the potential risks with the product and how this compares with the safety profile of current authorised medicinal products for the same condition. In particular a comparative discussion vis a vis ifosfamide would be relevant for the purpose of significant benefit justification.

In the written response, and during an oral explanation before the Committee on 3 October 2012, the sponsor elaborated with regards to medical plausibility, and discussed that the model presented in the application can be considered relevant because it spontaneously metastasizes similarly to the proposed condition and has been used in the development of many other chemotherapeutic agents. Furthermore, the sponsor argued that available clinical data with a precursor compound in patients

with the condition support the assumption of medical plausibility. With regards to the significant benefit, the sponsor discussed available preliminary clinical phase I data with the product in combination with carboplatin and etoposide, and argued on improved safety.

The Committee noted that the abovementioned preclinical model is described in the literature as a non-small cell lung cancer model and that existing models small cell cancer exist. More importantly, no specific non-clinical or clinical evidence has been provided to support the claims of an improved safety and efficacy versus the mother medicinal product.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 3 October 2012, prior to final opinion.

2.1.4 For treatment of hepatic encephalopathy - EMA/OD/101/12

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

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

- Proposed orphan indication

The sponsor was invited to elaborate on hepatic encephalopathy as a distinct medical entity versus being a manifestation of several underlying medical entities, taking into account the pathogenesis and all the possible aetiologies leading to hepatic encephalopathy.

- Prevalence

The sponsor was invited to further elaborate on the exclusion from the calculation of prevalence of: causes of hepatic encephalopathy other than cirrhosis; stages or different severities of hepatic encephalopathy such as e.g. minimal hepatic encephalopathy. The sponsor was also invited to recalculate the prevalence including all the excluded aetiologies and stages of hepatic encephalopathy.

- Significant benefit

The sponsor was invited to elaborate on the significant benefit of the proposed product, taking into account the paucity of data on long-term outcomes, especially on survival. In addition, the sponsor was invited to further discuss the possible role of concomitant treatments (e.g. lactulose and treatments used in hepatic encephalopathy caused by acute liver failure) in the results of the clinical studies, and the possible confounding by concomitant causal factors (e.g. benzodiazepine intoxication).

The sponsor was asked also to justify bridging the clinical data obtained in bibliographic studies with the intravenous formulation with the proposed sublingual formulation.

In the written response, and during an oral explanation before the Committee on 3 October 2012, the sponsor revised the orphan indication to a subset of the initial proposal and in particular "overt hepatic encephalopathy". It was argued that patients with minimal hepatic encephalopathy have no recognizable clinical symptoms of hepatic encephalopathy and that minimal encephalopathy is not a clinical entity. Furthermore, for the purpose of calculation of prevalence acute liver failure was excluded on the grounds that the product is not considered to have a place in the treatment of these patients.

The Committee considered that the sponsor's arguments for the justification of overt hepatic encephalopathy as a distinct entity (disorder affecting the brain, distinct presentation and pathophysiology) indicate that the proposed condition is a symptom of other underlying disorders. In

addition, the committee also considered that selecting subsets of the proposed condition contradicts the explicit provisions of ENTR/6283/00 Rev 03 as "*different degrees of severity or stages of a disease would generally not be considered as distinct conditions*" and "*the fact that a subset of patients exists in whom the medicinal product is expected to show a favourable benefit/risk would generally not be sufficient to define a distinct condition*".

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 3 October 2012, prior to final opinion.

2.1.5 IL-12 secreting dendritic cells, loaded with autologous tumor lysate for treatment of malignant glioma, Activartis Biotech GmbH - EMA/OD/092/12

[Co-ordinators: D. O'Connor / L. Fregonese]

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

- Proposed indication

The COMP has previously designated glioma as distinct medical entity. The sponsor was invited to broaden the condition from "malignant glioma" to "glioma".

- Medical plausibility

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

- the product's relevance for the treatment of glioma;

- the relevance of the preclinical model used to the treatment of glioma. Regarding this model, the sponsor was also invited to better describe the results of the tumour growth.

The sponsor was invited to present any available clinical data in glioma.

- Prevalence

The sponsor was invited to re-calculate the prevalence based on relevant epidemiological studies and registries for the proposed orphan condition in the EU, using European sources. The sponsor was reminded that the prevalence calculation should reflect the orphan indication as proposed, i.e. if the indication is broadened to "treatment of glioma", all glioma should be taken into account in the prevalence calculations.

- Significant benefit

The sponsor was invited to discuss the significant benefit of the proposed product in relation to existing satisfactory treatments for the disease, including authorized antineoplastic medicinal products and other satisfactory methods such as surgery.

In the written response, and during an oral explanation before the Committee on 3 October 2012, the sponsor further elaborated on in *vitro/ex vivo* experiments showing that immune responses were elicited after treatment with the proposed dendritic cell-based product in some solid and haematologic cancers. The sponsor also presented a new prevalence estimate based on Globocan data and discussed the on-going clinical trial in glioblastoma. The sponsor presented preliminary data on overall survival and progression free survival.

For the purpose of orphan designation, the COMP considered that the indication should be broadened to "treatment of glioma".

The Committee agreed that the condition, glioma, is a distinct medical entity and meets the criteria for orphan designation. Glioma was estimated to be affecting approximately 1 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to symptoms caused by compression of brain tissue by the tumour, and by blocking of the cerebrospinal fluid circulation. The compression causes generalized symptoms such as headache, anorexia, nausea, vomiting, seizures, drowsiness, mood disturbances and cognitive slowing, and focal symptoms such as difficulties with hearing, vision, speech, ambulation, dexterity, and hemiparesis. Glioma is a fatal disease, with 5-year mortality figures up to 90%. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that IL-12-secreting dendritic cells, loaded with autologous tumour lysate may be of significant benefit to those affected by the condition. The significant benefit is based on a new mechanism of action that enhances the specific immune T-lymphocytes response against the tumour. This has the potential to translate into clinical efficacy as suggested by preliminary clinical results showing survival advantage of IL-12-secreting dendritic cells treatment versus control during 18 months of treatment.

A positive opinion for IL-12-secreting dendritic cells, loaded with autologous tumour lysate, for treatment of glioma, was adopted by consensus.

2.1.6 **Milciclib Maleate** for treatment of thymic epithelial tumors, Nerviano Medical Science Srl - EMA/OD/093/12

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

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

- Medical Condition

Thymic epithelial tumours should be justified as a distinct medical entity or the application should be changed accordingly.

The proposed indication appears to span both malignant and benign conditions, with different histological and clinical features as well as classification codes. Therefore the sponsor was asked to justify why they are pooled together into one proposed indication.

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the medicine, for the treatment of thymic epithelial tumours, the sponsor was also invited to further elaborate on the particulars and the assessments of the two responders and on any preliminary data from clinical studies. As there are validated models to study the effects of products on this condition the sponsor was invited to elaborate further on the lack of pre-clinical data.

- Prevalence

The sponsor was requested to clarify whether benign neoplasms of the thymus have also been accounted for. A revised calculation may be needed in case of an updated indication.

In its written response, and during an oral explanation before the Committee on 3 October 2012, the sponsor recognised that there are different classifications for benign and malignant tumours. Nevertheless, the sponsor proposed to retain the indication covering all thymic epithelial tumours. With

regards to the medical plausibility, the sponsor discussed some new data from in vitro experiments and preliminary observations from clinical studies showing positive results in cell lines and patients with malignant thymoma.

For the purpose of orphan designation, the COMP considered that the indication should be renamed as "treatment of malignant thymoma".

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

The intention to treat malignant thymoma was considered justified on the grounds of preliminary clinical data in patients with the condition. The condition was estimated to be affecting approximately 0.12 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating and life-threatening based on 5-year overall survival that has been reported as low as 23% depending on the histological type. There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for milciclib maleate, for treatment of malignant thymoma, was adopted by consensus.

2.1.7 For treatment of myelodysplastic syndrome - EMA/OD/051/12

[Co-ordinators: R. Elbers / S. Tsigkos]

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

- Medical plausibility

To establish if a scientific rationale exists for the development of the product for treatment of myelodysplastic syndrome, the sponsor was invited to further elaborate on the applicability of the results obtained in vitro for drawing conclusions on the treatment of myelodysplastic syndrome in a clinically relevant context. The sponsor was asked to provide data from relevant models to support the plausibility of the product's use in the clinical setting, since the COMP considers this to be an essential requirement.

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the in vitro studies to justify the assumption of significant benefit over authorised medicinal products e.g. erythropoietin for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 3 October 2012, the sponsor argued that even though animal models have been described in the literature for myelodysplastic syndromes (MDS), all of them pertain to high risk patients that are phenotypically close to acute leukaemia, and that none would be appropriate to use for the population that the product was targeting. The sponsor also elaborated on the available ex vivo data using bone marrow samples from MDS patients that showed an increase in the number of erythroid precursors. The sponsor expected this to translate in an increase of haemoglobin levels resulting in a reduction on transfusion frequency. According to the sponsor this would also constitute a clinically relevant

advantage of improved efficacy versus existing satisfactory treatments, in particular for low risk patients.

The Committee considered that the available models would be appropriate for the proposed condition as applied for designation and that with regards to the arguments provided for significant benefit, the ex vivo data discussed could not allow for extrapolation of the clinically relevant advantage versus currently available satisfactory treatments.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 5 October 2012, prior to final opinion.

2.1.8 For treatment of Friedreich's ataxia - EMA/OD/096/12
[Co-ordinators: V. Stoyanova / L. Fregonese]

The Committee noted the withdrawal of the application prior to responding to the COMP list of questions.

2.2. For discussion / preparation for an opinion

2.2.1 Adeno-associated viral vector encoding an inducible short hairpin RNA targeting claudin-5 (prior to administration of 17-dimethylaminoethylamino-17-demethocygeldanamycin) for treatment of retinitis pigmentosa, Avena Therapeutics Ltd - EMA/OD/135/12
[Co-ordinators: V. Saano / S. Tsigkos]

The Committee agreed that the condition, retinitis pigmentosa, is a distinct medical entity and meets the criteria for orphan designation. Retinitis pigmentosa was estimated to be affecting less than 3.7 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to the development of nyctalopia (night blindness) and tunnel vision that progresses to total blindness. There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for adeno-associated viral vector encoding an inducible short hairpin RNA targeting claudin-5 (prior to administration of 17-dimethylaminoethylamino-17-demethoxygeldanamycin), for treatment of retinitis pigmentosa, was adopted by consensus.

2.2.2 For treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated) - EMA/OD/104/12
[Co-ordinators: D. O'Connor / L. Fregonese]

The Committee considered that the prevalence requires clarification by the sponsor. The sponsor calculated prevalence from incidence data and the estimated duration of the disease. The prevalence is considered by the sponsor to be 0.075 in 10,000 people, which is much lower than previous estimates for this condition, and the duration of the disease data are from the US and not from the EU. The sponsor is invited to re-calculate the prevalence using updated sources, and relevant European sources.

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

2.2.3 Alisertib sodium (alisertib) for treatment of ovarian cancer, Takeda Global Research and Development Centre (Europe) Ltd - EMA/OD/114/12
[Co-ordinators: B. Bloechl-Daum / L. Fregonese]

The Committee agreed that the condition, ovarian cancer, is a distinct medical entity and meets the criteria for orphan designation. Ovarian cancer was estimated to be affecting not more than 3 in 10,000 people in the European Union, at the time the application was made. The condition is life-threatening and chronically debilitating due to early spread of the cancer to the rest of the peritoneal cavity. Most patients have widespread disease at presentation. Symptoms such as abdominal pain and swelling, gastrointestinal symptoms, and pelvic pain often go unrecognized, leading to delays in diagnosis. Yearly mortality in ovarian cancer is approximately 65% of the incidence rate. Long-term follow-up of stage III and stage IV patients showed a 5-year survival rate of less than 10%. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that alisertib may be of significant benefit to those affected by the condition. Preclinical results showed improved antineoplastic activity when the product was used in combination with medicinal products currently authorized for the treatment of ovarian cancer in the EU. Early clinical results showed a favorable survival in a small group of patients with platinum refractory/resistant ovarian cancer. This is assumed to translate into a clinically relevant advantage based on the potential use of the product in combination with currently authorized treatments and in patients who are refractory/resistant to currently authorized treatments.

A positive opinion for alisertib, for treatment of ovarian cancer, was adopted by consensus. The draft Summary Report was updated in line with the discussion and the draft Opinion circulated.

2.2.4 For treatment of acquired aplastic anaemia - EMA/OD/100/12
[Co-ordinators: R. Elbers / S. Tsigkos]

The Committee has considered that by the data and arguments provided so far by the sponsor, the criteria for orphan designation as provisioned cannot be considered met. The Committee considered that the following issues require clarification by the sponsor:

- Description of the condition

Acquired aplastic anaemia should be justified as a distinct medical entity or the indication should be changed accordingly. In particular the company is asked to explain why the proposed product might not work in other forms of aplastic anaemia.

- Medical plausibility

To establish if a scientific rationale exists for the development of the product for treatment of aplastic anaemia, the sponsor is invited to further elaborate on:

- the proposed mechanism of "retro-differentiation",

- the absence of any preclinical models in the condition as applied for (acquired aplastic anaemia),

- the referenced clinical data, including a detailed account of the underlying conditions, previous treatments received and the uncontrolled nature of the observations.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life threatening or chronically debilitating nature of the condition. From the data provided and the sponsor's arguments it is not well substantiated that the condition represents a life threatening or chronically debilitating condition.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation.

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

- Existing methods of treatment

The sponsor is invited to perform a search through EU national formularies and central databases and confirm any existing authorised products for the proposed indication as applied for. If non-pharmacologic methods, as for example haematopoietic stem cell transplantation and agents to support these procedures, are considered satisfactory, adequate argumentation is to be provided in the application.

- Justification of significant benefit

In the absence of a justified medical plausibility the significant benefit cannot be considered. In case the sponsor submits further arguments for the medical plausibility section, the significant benefit should also be further elaborated versus the existing satisfactory methods of treatment and supported by any available scientific results.

A comparative discussion versus non-pharmacologic treatments, e.g. stem cell transplantation is also expected to be provided

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

2.2.5 **Canakinumab** for treatment of TNF-receptor associated periodic syndrome (TRAPS), Novartis Europharm Limited - EMA/OD/060/12

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

The Committee agreed that the condition, tumour necrosis factor receptor-associated periodic syndrome (TRAPS), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the proposed condition appears justified based on preliminary clinical data in TRAPS patients. Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) was estimated to be affecting approximately 0.01 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to recurrent episodes of fever, abdominal pain, arthralgias, myalgias, rash, conjunctivitis, periorbital oedema, and development of amyloid nephropathy. There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for canakinumab, for treatment of tumour necrosis factor receptor-associated periodic syndrome (TRAPS), was adopted by consensus.

2.2.6 Chimeric monoclonal antibody against GD2 for treatment of neuroblastoma, APEIRON Biologics AG - EMA/OD/112/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

The intention to treat neuroblastoma was considered justified based on preliminary clinical data in neuroblastoma patients. The condition was estimated to be affecting approximately 1.1 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating and life threatening with a 5-year survival of approximately 50%. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that chimeric monoclonal antibody against GD2 may be of significant benefit to those affected by the condition. This appears justified in particular with regards to a potential clinically relevant advantage based on the alternative mechanism of action which may lead to improved effect. This is supported by preliminary clinical data.

A positive opinion for chimeric monoclonal antibody against GD2, for treatment of neuroblastoma, was adopted by consensus.

2.2.7 For treatment of acromegaly - EMA/OD/107/12
[Co-ordinators: K. Westermark / S. Tsigkos]

The Committee considered that the significant benefit requires clarification by the sponsor. The arguments on significant benefit are based on the potentially improved efficacy and safety in the condition, based on preclinical comparisons to octreotide. In the preclinical settings discussed, the sponsor is requested to further elaborate on the product's activity and GH response in adenoma cells tested.

The sponsor is also requested to elaborate on the clinical relevance of the proposed safety profile in the in vivo preclinical studies. The grounds on which the preclinical data presented are expected to be translated into a clinically relevant advantage should be discussed.

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

2.2.8 For treatment of squamous cell carcinoma of the head and neck - EMA/OD/120/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the proposed mechanism of action. In particular, the kinetics of the proposed product, including the selective uptake by the tumour cells, is to be further discussed.

- Prevalence

The sponsor is invited to re-calculate the prevalence based on a justified duration of the 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. 5-year prevalence data are also expected.

- Justification of significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit versus authorised products for the proposed condition as applied for.

The sponsor should position the proposed treatment in the current management of head and neck patients and provide data to justify a clinically relevant advantage or a major contribution to patient care.

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

2.2.9 **Erdosteine** for treatment of mercury toxicity, Rafifarm SRL - EMA/OD/119/12

[Co-ordinators: M. Možina / S. Mariz]

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

Mercury toxicity was estimated to be affecting less than 1 in 10,000 people in the European Union, at the time the application was made. This is based on a literature search. The condition is chronically debilitating due to symptoms such as unsteadiness of gait and limbs, muscle weakness, irritability, memory loss, depression and sleeping difficulties. It is life-threatening when there is acute exposure to high doses. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that erdosteine may be of significant benefit to those affected by the condition. This appears justified with regards to a clinically relevant advantage and is supported by comparative data to *N*-acetyl-*L*-cysteine in two non-clinical models where toxicity was induced with mercury chloride showing improved survival.

A positive opinion for erdosteine, for treatment of mercury toxicity, was adopted by consensus.

2.2.10 **Ixazomib** for treatment of systemic light chain amyloidosis, Takeda Global Research and Development Centre (Europe) Ltd - EMA/OD/110/12

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

The Committee agreed that the condition, systemic light chain amyloidosis, is a distinct medical entity and meets the criteria for orphan designation.

Systemic light chain amyloidosis was estimated to be affecting approximately 0.7 in 10,000 people in the European Union, at the time the application was made; the sponsor has based their prevalence calculation on an extensive literature search. The condition is chronically debilitating due to the accumulation of extracellular amyloidogenic fibril deposits which disrupts normal tissue structure and function, notably in the heart, kidneys, liver, peripheral nervous system, gastrointestinal tract, and soft tissues. The disease carries a poor prognosis, predominantly influenced by the patient's performance status and extent of organ involvement, particularly cardiac involvement, at diagnosis. As such, the majority of patients with AL amyloidosis die from cardiac death, which is often sudden. There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for ixazomib, for treatment of systemic light chain amyloidosis, was adopted by consensus.

2.2.11 Melarsoprol-Hydroxypropylbetadex for treatment of trypanosomiasis, Pr. Peter Kennedy - EMA/OD/116/12
[Co-ordinators: V. Stoyanova / S. Mariz]

For the purpose of orphan designation, the COMP considered that the treatment of trypanosomiasis should be restricted to "the treatment of African trypanosomiasis".

The Committee agreed that the condition, African trypanosomiasis, is a distinct medical entity and meets the criteria for orphan designation. African trypanosomiasis was estimated to be affecting approximately 0.00004 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 condition is chronically debilitating due to the extensive damage seen during the first haemolymphatic phase of the condition which leads to arrhythmias, anaemia, endocrine, cardiac, and kidney dysfunctions. Moreover, in the second (neurological) phase the parasite invades the central nervous system by passing through the blood–brain barrier. In this phase symptoms include confusion, impaired coordination, and disruption of the sleep cycle, with bouts of fatigue punctuated with manic periods, leading to daytime slumber and night-time insomnia. Without treatment, the disease is invariably fatal, with progressive mental deterioration leading to coma and death. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that melarsoprol may be of significant benefit to those affected by the condition. This appears justified in particular with regards to a major contribution to patient care based on the development of an oral formulation and the potential to reduce the toxicity associated with the active substance. This is based on preliminary data using a valid preclinical model which showed a reduction in the toxicity when the oral formulation is used.

A positive opinion for melarsoprol, for treatment of African trypanosomiasis, was adopted by consensus.

2.2.12 For treatment of acanthamoeba keratitis - EMA/OD/090/12
[Co-ordinators: S. Thorsteinsson / S. Tsigkos]

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

- Medical plausibility

In the absence of any data with the product as applied for, medical plausibility in the proposed condition cannot be considered. Any available data with the proposed product in a relevant model or clinical setting as applied for designation should be provided to the Committee.

In addition, the sponsor is requested to discuss the relevance of referring to the previous designations for each one of the constituents of the proposed combination alone in the current application and elaborate on the rationale to combine the two active substances into a single product.

The sponsor should provide any available data with the combination (and not with the individual constituents separately) in order to justify the medical plausibility.

In the absence of these justifications, the intention to treat the proposed condition may not be considered justified by the Committee.

- Development of Medicinal Product

The sponsor should further clarify the development plan for the combination as proposed.

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

Post-meeting note: *the sponsor withdrew the application on 22 October 2012.*

2.2.13 Naloxone hydrochloride dihydrate for treatment of cutaneous T-cell lymphoma, Winston Laboratories Ltd - EMA/OD/050/12
[Co-ordinators: K. Westermark / S. Tsigkos]

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

The intention to treat Cutaneous T-cell lymphoma appears justified based on preliminary clinical data in patients affected by the condition that show a reduction in disease-associated pruritus . The condition was estimated to be affecting less than 2.6 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to persistent symptoms such as ulceration, erythroderma and pruritus and life-threatening due to systemic infections and further malignant transformation. In particular, all stages of the condition may include chronic persistent pruritus, sometimes of profound severity, often accompanied by self-inflicted excoriation of the pruritic areas and bacterial colonization of the ulcerated skin. Systemic infections secondary to the excoriation are a major contributor to morbidity and mortality. Chronic intractable pruritus has a significant detrimental impact on quality of life, and for individuals with mycosis fungoides it has been reported to double the mortality rate compared to those without pruritus. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that topical administration of naloxone hydrochloride dihydrate may be of significant benefit to those affected by the condition on the grounds of a major contribution to patient care. This appears justified on the grounds of a preliminary clinical study showing a reduction in disease-associated pruritus, considering that pruritus is a characteristic of the condition, independent of the stage of the disease and its serious consequences.

A positive opinion for naloxone hydrochloride dihydrate, for treatment of cutaneous T-cell lymphoma, was adopted by consensus.

2.2.14 Panobinostat for treatment of multiple myeloma, Novartis Europharm Limited - EMA/OD/113/12
[Co-ordinators: V. Saano / S. Mariz]

The Committee agreed that the condition, multiple myeloma, is a distinct medical entity and meets the criteria for orphan designation. Multiple myeloma was estimated to be affecting not more than 3.2 in 10,000 people in the European Union, at the time the application was made. This was based on the Globocan and Nordcan Registries. The condition is life-threatening and chronically debilitating due to the accumulation of monoclonal myeolomatous cells in the bone marrow, causing disruption of the normal bone marrow function with pancytopenia and osteolysis. Opportunistic infections, hypercalcemia, and kidney failure are common clinical consequences of the disease. The median survival is 5 years. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that panobinostat may be of

significant benefit to those affected by the condition. The product is a pan-HDAC inhibitor of Class I, II and IV histone deacetylases (HDACs) which is involved in the deacetylation of histone and non-histone cellular proteins. The combination of bortezomib, panobinostat and dexamethasone resulted in synergistic effects seen on apoptosis and growth inhibition in both the *in vitro* and *in vivo* models. Preliminary clinical data has shown that the product can be used in combination with established therapies in the treatment of refractory and relapsed multiple myeloma.

A positive opinion for panobinostat, for treatment of multiple myeloma, was adopted by consensus.

2.2.15 Recombinant human dyskerin for treatment of dyskeratosis congenita, Advanced Medical Projects - EMA/OD/136/11
[Co-ordinators: A. Corrêa Nunes / S. Mariz]

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

Dyskeratosis congenita was estimated to be affecting approximately 0.01 in 10,000 persons in the European Union, at the time the application was made; the sponsor has used two publications to support the prevalence calculation for the condition. The condition is chronically debilitating due to bone marrow failure resulting in peripheral cytopenias. It has been shown that 85% of dyskeratosis congenita patients have a peripheral cytopenia of one or more lineages, with approximately 75% of these patients developing pancytopenia. It is life-threatening due to malignant disease which is also reported in dyskeratosis congenita including, solid tumours of the tongue, buccal mucosa, nasopharynx, rectum, cervix, vagina, skin, esophagus and pancreas. These features include bone marrow failure, pulmonary disease, and ophthalmic, skeletal, dental, genitourinary, gastrointestinal, haematological and neurological abnormalities. Pulmonary complications have also been reported to develop in approximately 20% of dyskeratosis congenita patients, resulting in reduced diffusion capacity with or without a restrictive defect. Mortality rate from these pulmonary complications has been estimated at between 10% and 15%. There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for recombinant human dyskerin, for treatment of dyskeratosis congenita, was adopted by consensus.

2.2.16 For treatment of follicular lymphoma - EMA/OD/076/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit. In particular the sponsor should discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

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

2.2.17 For treatment of hairy cell leukemia - EMA/OD/082/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit. In particular the sponsor should discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

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

Post-meeting note: *the sponsor withdrew the application on 12 October 2012.*

2.2.18 For treatment of B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma - EMA/OD/083/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit. In particular the sponsor should discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

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

2.2.19 For treatment of mature B-cell lymphoma: plasma cell lymphoma/plastocytoma - EMA/OD/080/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life threatening or chronically debilitating nature of the condition as proposed.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation. The sponsor is invited to re-calculate the prevalence based on relevant epidemiological studies and registries 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. It is noted that incidence and prevalence are different epidemiological measures.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit.

In particular the sponsor should discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

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

Post-meeting note: *the sponsor withdrew the application on 12 October 2012.*

2.2.20 For treatment of splenic marginal zone B-cell lymphoma - EMA/OD/079/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life threatening or chronically debilitating nature of the condition as proposed.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation. The sponsor is invited to re-calculate the prevalence based on relevant epidemiological studies and registries 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. It is noted that incidence and prevalence are different epidemiological measures.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit. In particular the sponsor should discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

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

Post-meeting note: *the sponsor withdrew the application on 12 October 2012.*

2.2.21 For treatment of mantle cell lymphoma - EMA/OD/077/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit. In particular the sponsor should discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed, and position the proposed product in the current management of these patients.

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

2.2.22 For treatment of Burkitt lymphoma - EMA/OD/075/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life threatening or chronically debilitating nature of the condition as proposed.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation.

The sponsor is invited to re-calculate the prevalence based on relevant epidemiological studies and registries 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. It is noted that incidence and prevalence are different epidemiological measures.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit. In particular the sponsor should discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

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

Post-meeting note: *the sponsor withdrew the application on 12 October 2012.*

2.2.23 For treatment of lymphoplasmacytic lymphoma - EMA/OD/081/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of sertraline for treatment of lymphoplasmacytic lymphoma the sponsor is invited:

- to further elaborate on the relevance of the preclinical model used for the treatment of lymphoplasmacytic lymphoma,

- to present any available data specific for the condition as proposed.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life threatening or chronically debilitating nature of the condition as proposed.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation.

The sponsor is invited to re-calculate the prevalence based on relevant epidemiological studies and registries 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. It is noted that incidence and prevalence are different epidemiological measures.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit. In particular the sponsor should:

- discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed, and

- position the proposed product in the current management of these patients.

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

Post-meeting note: *the sponsor withdrew the application on 12 October 2012.*

2.2.24 For treatment of B-cell prolymphocytic leukemia - EMA/OD/074/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life threatening or chronically debilitating nature of the condition as proposed.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation.

The sponsor is invited to re-calculate the prevalence based on relevant epidemiological studies and registries 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. It is noted that incidence and prevalence are different epidemiological measures.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit. In particular the sponsor should discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

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

Post-meeting note: *the sponsor withdrew the application on 12 October 2012.*

2.2.25 For treatment of diffuse large B-cell lymphoma - EMA/OD/073/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit. In particular the sponsor should discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

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

2.2.26 For treatment of Extranodal Marginal Zone B-cell Lymphoma of the MALT type - EMA/OD/072/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life threatening or chronically debilitating nature of the condition as proposed.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation.

The sponsor is invited to re-calculate the prevalence based on relevant epidemiological studies and registries 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. It is noted that incidence and prevalence are different epidemiological measures.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit. In particular the sponsor should discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

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

Post-meeting note: *the sponsor withdrew the application on 12 October 2012.*

2.2.27 For treatment of nodal marginal zone B-cell lymphoma ± monocytoid - EMA/OD/078/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- Medical plausibility

The sponsor is requested to further elaborate on the medical plausibility, and in particular to discuss:

- the relevance of the preclinical model to draw conclusions for the specific condition subject of this application;

- the pharmacodynamic characteristics of the product regarding specificity to the identified target cells in the proposed mechanism of action;

- the consequences of the dose used in the model in relation to the dose expected for development and its potential implications in terms of safety.

- Life-threatening and debilitating nature of the condition

The sponsor should further elaborate on the life threatening or chronically debilitating nature of the condition as proposed.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation.

The sponsor is invited to re-calculate the prevalence based on relevant epidemiological studies and registries 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. It is noted that incidence and prevalence are different epidemiological measures.

- Justification of significant benefit

The sponsor is requested to further elaborate on the justification of significant benefit. In particular the sponsor should discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed.

- discuss how the preclinical data presented in this application can be translated into a clinically relevant advantage or major contribution to patient care compared to currently authorised products for the condition as proposed, and

- position the proposed product in the current management of these patients.

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

Post-meeting note: *the sponsor withdrew the application on 12 October 2012.*

2.2.28 Synthetic double-stranded siRNA oligonucleotide directed against Claudin-5 complexed with polyethyleneimine (prior to administration of doxorubicin) for treatment of glioma, Avena Therapeutics Ltd - EMA/OD/136/12
[Co-ordinators: R. Elbers / S. Mariz]

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

Glioma was estimated to be affecting less than 2.2 in 10,000 persons in the European Union, at the time the application was made; this is based on the Irish and Norwegian Cancer registries search. This is not more than 5 in 10,000 people as established in Article 3(1) (a) of Regulation (EC) 141/2000. The condition is chronically debilitating due to symptoms associated with the location of the glioma, a central nervous system glioma can cause headaches, nausea and vomiting, seizures, and cranial nerve disorders as a result of increased intracranial pressure. A glioma of the optic nerve can cause visual loss. Spinal cord gliomas can cause pain, weakness, or numbness in the extremities. Gliomas are life-threatening, in particular due to a significant reduction of survivability. Of patients diagnosed each year with malignant gliomas, about half are alive 1 year after diagnosis, and 25% after two years. This is dependent on the type with glioblastoma multiforme having the worst prognosis with many patients surviving less than 1 year. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that synthetic double-stranded siRNA oligonucleotide directed against claudin-5 complexed with polyethyleneimine (administered prior to doxorubicin) may be of significant benefit to those affected by the condition. This was based on a clinically relevant advantage which is supported by two pre-clinical glioblastoma models showing increased survival and reduction in tumour size compared to controls.

A positive opinion for synthetic double-stranded siRNA oligonucleotide directed against claudin-5 complexed with polyethyleneimine (prior to administration of doxorubicin), for treatment of glioma, was adopted by consensus.

2.2.29 Tafamidis (Vyndaqel) for treatment of senile systemic amyloidosis, Pfizer Limited - EMA/OD/115/12
[Co-ordinators: J. Torrent-Farnell / S. Mariz]

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

Senile systemic amyloidosis was estimated to be affecting approximately 3 in 10,000 people in the European Union, at the time the application was made. The sponsor has based their evaluation of the prevalence in Europe on a literature search. The condition is life-threatening. Actual median survival rates from diagnosis for patients with the condition are approximately 60 months. Most patients (42-71%) die from cardiac causes, including sudden death, congestive heart failure and myocardial infarction. There is, at present, no satisfactory treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for tafamidis, for treatment of senile systemic amyloidosis, was adopted by consensus.

2.2.30 Tralokinumab for treatment of idiopathic pulmonary fibrosis, MedImmune Ltd - EMA/OD/111/12
[Co-ordinators: V. Saano / L. Fregonese]

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

Idiopathic pulmonary fibrosis was estimated to be affecting not more than 3 in 10,000 people in the European Union, at the time the application was made. The condition is life-threatening and chronically debilitating due to progressive dyspnoea and loss of lung function, severely limiting exercise capacity and deteriorating quality of life of the affected patients, leading in many cases within months or a few years to the need of oxygen therapy and lung transplantation. Median survival without transplantation is less than five years. Death ultimately occurs due to respiratory failure. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that tralokinumab may be of significant benefit to those affected by the condition. The significant benefit is based on a new mechanism of action, specifically targeting interleukin 13, one of the mediators involved in fibrogenesis in idiopathic pulmonary fibrosis. The potential of this mechanism to translate into clinical efficacy is mainly supported by a study showing improvement of established lung fibrosis in a pulmonary fibrosis model treated with tralokinumab.

A positive opinion for tralokinumab, for treatment of idiopathic pulmonary fibrosis, was adopted by consensus.

2.2.31 For treatment of non-infectious uveitis - EMA/OD/118/12
[Co-ordinators: V. Stoyanova / S. Tsigkos]

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

- Medical plausibility

In view of the results of the earlier presented pivotal studies, the sponsor is asked to elaborate on the medical plausibility, by providing any available preliminary data from the additional phase 3 study.

- Prevalence

The sponsor should provide a comparative discussion on the prevalence of non-infectious uveitis versus the prevalence of chronic-non-infectious uveitis.

The sponsor should explain the discrepancy between the calculations presented in the previous designation held by the sponsor which is understood as a subset of the current indication and consequently should have a lower prevalence estimate.

- Justification of significant benefit

The justification of significant benefit is argued on the basis of improved safety of the product versus cyclosporin, on a comparative trial in psoriasis. The sponsor is invited to further elaborate on this comparison and clearly justify how these data may be translated into a clinically relevant advantage or a major contribution to patient care.

In addition the sponsor is invited to position the proposed product in the current management of non-infectious uveitis patients, by providing a comparative discussion versus all authorised products.

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

2.3. Evaluation on-going

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

2.4. Validation on-going

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

3. Requests for protocol assistance

3.1 Treatment of acute myeloid leukaemia [Co-ordinator: B. Bloech-Daum]

The protocol assistance was adopted by the Committee.

3.2 Treatment of acute myeloid leukaemia [Co-ordinator: R. Elbers]

The protocol assistance letter was adopted by the Committee.

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 16 upcoming applications.

4.2 Update on orphan applications for Marketing Authorisation

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

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 NexoBrid (purified bromelain) for treatment of partial deep dermal and full thickness burns; Teva Pharma GmbH (OD/012/02, EU/3/02/107) [Co-ordinators: J. Eggenhofer / S. Tsigkos].

The Committee considered that the significant benefit requires clarification by the sponsor.

The sponsor is invited to further elaborate on the justifications provided for significant benefit. In particular a clinically relevant advantage or a major contribution to patient care should be justified in comparison to currently authorised products and the current standard of care.

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

5.1.2 Adcetris (Monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin E) Takeda Global Research and Development Centre (Europe) Ltd [Co-ordinators: V. Stoyanova / S. Tsigkos].

The Committee adopted the public summaries of the opinions on the review of the orphan designation (adopted at the September meeting):

- EMA/COMP/601841/2012 for treatment of Hodgkin lymphoma (OD/073/08, EU/3/08/596)
- EMA/COMP/601842/2012 for treatment of anaplastic large cell lymphoma (OD/072/08, EU/3/08/595).

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

5.2.1 Bosulif (Bosutinib) for treatment of chronic myeloid leukaemia; Pfizer Limited (OD/160/09, EU/3/10/762) [Co-ordinators: R. Elbers / S. Tsigkos].

5.2.2 Defitelio (Defibrotide) for prevention of hepatic veno-occlusive disease (OD/025/04, EU/3/04/211) and for treatment of hepatic veno-occlusive disease (OD/026/04, EU/3/04/212); Gentium S.p.A. [Co-ordinators: J. Torrent-Farnell / S. Mariz]

5.2.3 Exjade (4-(3,5-bis(hydroxy-phenyl)-1,2,4) triazol-1-yl) benzoic acid) for treatment of chronic iron overload requiring chelation therapy; Novartis Europharm Limited (OD/061/01, EU/3/02/092) [Co-odinators: M. Mozina/ S. Mariz]
Type II variations – new indications:

- treatment of infrequently transfused beta-thalassemia major patients;
- treatment of non-transfusion dependent thalassemia syndromes.

5.2.4 Jenzyl ((1R, 2R, 4S)-4-{(2R)-2-[(3S,6R,7E,9R,10R,12R,14S,15E,17E,19E,21S,23S,26R, 27R,34aS)-9,27-dihydroxy-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-1,5,11,28,29-pentaoxo-1,4,5,6,9,10,11,12,13,14,21,22,23,24,25,26,27,28,29,31,32,33,34,34a-tetra-cosahydro-3H-23,27-epoxypyrido[2,1-c][1,4]oxazacyclohentriacontin-3-yl]propyl}-2-methoxy-cyclohexyldimethyl-phosphinate) for treatment of soft tissue sarcoma (OD/050/05, EU/3/05/312) and for treatment of primary malignant bone tumours (OD/055/05, EU/3/05/321); Merck Sharp & Dohme Limited [Co-ordinators: B. Dembowska-Baginska / L. Fregonese].

5.3. On-going procedures

5.3.1 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. (OD/024/05 , EU/3/05/314) [Co-ordinators: N. Sypsas / TBC]

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 (OD/080/09, EU/3/09/683) [Co-ordinators: A. Magrelli / TBC]

5.3.3 Cysteamine bitartrate [Cysteamine bitartrate (gastroresistant)] for treatment of cystinosis; Raptor Pharmaceuticals Europe B.V. (OD/034/10, EU/3/10/778) [Co-ordinators: V. Saano / S. Mariz]

5.3.4 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 (OD/094/07, EU/3/07/524); Otsuka Novel Products GmbH [Co-ordinators: V. Stoyanova / L. Fregonese]

5.3.5 Iclusig (benzamide, 3-(2-imidazo[1,2-b]pyridazin-3-ylethynyl)-4-methyl-N-[4-[(4-methyl-1-piperazinyl)methyl]-3-(trifluoromethyl)phenyl]-); ARIAD Pharma Ltd [Co-ordinators: K. Kubackova / TBC]

- treatment of chronic myeloid leukaemia (OD/121/09, EU/3/09/716);
- treatment of acute lymphoblastic leukaemia (OD/122/09, EU/3/09/715).

5.3.6 Istodax (previously Romidepsin) ((E)-(1S,4S,10S,21R)-7-[(Z)-ethylidene]-4,21-diisopropyl-2-oxa-12,13-dithia-5,8,20,23- tetraazabicyclo[8.7.6]tricos-16-ene-3,6,9,19,22-pentone) for treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated); Celgene Europe Limited (OD/056/05, EU/3/05/328) [Co-ordinators: D. O'Connor / L. Fregonese]

5.3.7 Kinaction (Masitinib mesilate) for treatment of pancreatic cancer; AB Science (OD/063/09, EU/3/09/684) [Co-ordinators: B. Bloechl-Daum/ TBC]

5.3.8 Loulla (Mercaptopurine) for treatment of acute lymphatic leukaemia, Only For Children Pharmaceuticals (OD/065/07, EU/3/07/496) [Co-ordinators: D. O'Connor / S. Tsigkos]

5.3.9 PAS-GR (Para-aminosalicylic acid) for treatment of tuberculosis; Lucane Pharma SA (OD/072/10, EU/3/10/826) [Co-ordinators: V. Stoyanova / S. Mariz]

5.3.10 Pheburane (Sodium phenylbutyrate) for treatment of carbamoyl-phosphate synthase-1 deficiency; Lucane Pharma SA (OD/098/11, EU/3/12/951) [Co-ordinators: J. Torrent-Farnell / TBC]

5.3.11 Pomalidomide Celgene (Pomalidomide) for treatment of multiple myeloma, Celgene Europe Ltd. (OD/053/09, EU/3/09/672) (Co-ordinators: R. Elbers/ S. Mariz]

5.3.12 Raxone (previously SAN Idebenone; Idebenone) for treatment of Leber's hereditary optic neuropathy; Santhera Pharmaceuticals (Deutschland) GmbH (OD/076/06, EU/3/07/434) [Co-ordinators: J. Torrent-Farnell / S. Mariz]

5.3.13 Revlimid (3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione) for treatment of myelodysplastic syndromes; Celgene Europe Limited – UK (OD/083/03, EU/3/04/192) [Co-ordinators: L. Gramstad / TBC]

5.3.14 Scenesse ([Nle4, D-Phe7]-alfa-melanocyte stimulating hormone, Afamelanotide) for treatment of erythropoietic protoporphyria; Clinuvel (UK) Limited (OD/108/07, EU/3/08/541) [Co-ordinators: L. Gramstad / S. Mariz]

5.3.15 Masican N-(methyl-diazacyclohexyl-methylbenzamide)-azaphenyl-aminothiopyrrole for treatment of malignant gastrointestinal stromal tumours; AB Science (OD/061/04, EU/3/04/251) [Co-ordinators: D. O'Connor / TBC]

5.3.16 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 (OD/020/02, EU/3/02/115) [Co-ordinators: S. Thorsteinsson / TBC]

6. Procedural aspects

6.1 Procedure for orphan medicinal product designation - Guidance for sponsors, http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/09/WC500003769.pdf

The revised guidance documents EMA/710916/2009 Rev. 6 was circulated for information.

6.2 European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP)

- The members were invited to put forward their candidatures for the COMP representative to the PCWP http://www.ema.europa.eu/ema/index.jsp?curl=pages/contacts/CHMP/people_listing_000017.jsp&mid=WC0b01ac0580028d32
- The presentation of the draft PCWP Work Plan for 2013, EMA/571572/2012 was postponed.

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

The presentation of the draft HCPWP Work Plan 2013, EMA/526726/2012 was postponed.

7. Any other business

7.1 EMA - FDA and EU - Japan collaboration

The Committee was reminded about the forthcoming FDA/EMA Orphan Designation and Grant Workshop to be held on 12-13 October 2012 in Washington D.C.

7.2 COMP Work Programme 2013-2015

The draft document EMA/COMP/600966/2012 was circulated in preparation for a discussion at the November meeting.

7.3 COMP Information Pack

The COMP Information Pack was circulated and tabled.

Date of next COMP meeting: 6 - 7 November 2012

Annex A

List of participants on 3-5 October 2012

Chair:
Bruno Sepodes

Vice-Chair:

Lesley Greene	Volunteer patient representative for Eurordis

COMP Members:

André Lhoir	België/Belgique/Belgien
Irena Bradinova	България
Kateřina Kubáčková	Česká Republika
Vacant	Danmark
Rembert Elbers	Deutschland
Vallo Tillmann	Eesti
Geraldine O'Dea	Éire/Ireland
Nikolaos Sypsas	Ελλάδα
Josep Torrent Farnell	España
Annie Lorence	France
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italia
Ioannis Kkolos	Κύπρος (present on 1st and 2nd day only)
Dainis Krievins	Latvija
Aušra Matulevičienė	Lietuva
Henri Metz	Luxembourg
Judit Eggenhofer	Magyarország
Albert Vincenti	Malta
Violeta Stoyanova	Nederland
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Österreich (present on 1st and 2nd day only)
Bożenna Dembowska-Bagińska	Polska
Ana Corrêa-Nunes	Portugal
Flavia Saleh	Romãnia
Martin Možina	Slovenija
Veijo Saano	Suomi/Finland
Kerstin Westermark	Sverige (present on 1st and 2nd day only)
Daniel O'Connor	United Kingdom
Pauline Evers	representing the European Genetic Alliances Network
Birthe Byskov Holm	volunteer patient representative for Eurordis
János Borvendég	CHMP Representative (present on 1st day only)
Aikaterini Moraiti	CHMP Representative
Vacant	EMA Representative

Observers:

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

EMA Secretariat:

Jordi Llinares Garcia	Head of Orphan Medicines Section
Laura Fregonese	Scientific Administrator

Segundo Mariz	Scientific Administrator
Stylianos Tsigkos	Scientific Administrator
Carla Paganin	EMA Expert
Federica Castellani	Scientific Administrator (Medical Information)
Agnieszka Wilk-Kachlicka	Assistant
Frederique Dubois	Assistant

Apologies:

Members:

Milica Molitorisová	Slovensko

Observers:

Antonio Blazquez	Agencia Española de Medicamentos y Productos Sanitarios
Ivana Martinovic	Croatia

European Commission:

Mirjam Soderholm	DG Health and Consumers