EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Development and Evaluation

Committee for Orphan Medicinal Products (COMP)

Minutes of the 5 - 6 February 2013 meeting

Note on access to documents

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

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1. Introduction

1.1 Adoption of the agenda EMA/COMP/16449/2013 Rev. 2

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 8 - 9 January 2013 EMA/COMP/790271/2012

The minutes were adopted.

1.3 Conflicts of Interest

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

The COMP secretariat was informed as follows:

- Eurordis receives funding from the sponsors who have submitted dossier to be considered for orphan designation at the current meeting (2.2.1, 2.2.3, 2.2.6, 2.2.11). Nevertheless, no direct conflicts of interest have been identified for L. Greene and B. Byskov Holm, who are the volunteer patient representatives for EURORDIS.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxamide monohydrate for treatment of hepatocellular carcinoma, Eli Lilly Nederland B.V. - EMA/OD/159/12
[Co-ordinators: R. Elbers (until 1 February 2013) / 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 hepatocellular carcinoma, the sponsor was invited to discuss the relevance of the in vitro studies on migration and aggregation of hepatocarcinoma cells to the proposed anti-tumour activity of the product, with particular regard to invasiveness and formation of metastasis.

In addition the sponsor was invited to further discuss the results of the clinical study Phase II in patients with hepatocellular carcinoma who have had disease progression on sorafenib or are not eligible to receive sorafenib, and in particular:

- the demographics, methodology and up to date results of this study including, among others, the number of cycles that the patients received up to date, the baseline levels of alpha fetoprotein and its

[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).

changes in the whole patient population, the results with respect to the primary endpoint of this study (time to progression).

- Justification of significant benefit

The sponsor was requested to further elaborate on the results from the clinical study phase II in order to explain how such results would support the claim of significant benefit over authorised medicinal products, e.g. sorafenib.

In the written response, and during an oral explanation before the Committee on 5 February 2013, the sponsor further elaborated on the Phase II clinical study, by discussing the results and clarifying the relevance of the endpoints used and the study population. The sponsor presented the results of the interim analysis of 106 patients with elevated alpha fetoprotein (AFP) levels.

The median time to progression in patients with elevated AFP was 12 weeks, which compares favourably to the 10.5 weeks which has been considered acceptable in second-line HCC treatment. As per the study protocol, the majority of patients had already received treatment with sorafenib, while the remaining patients were not eligible to receive sorafenib. It was explained by the sponsor that a number of patients (17) were truly sorafenib naïve, the reasons being that sorafenib had not been considered an appropriate treatment based on clinical reasons such as kidney disease.

Moreover, the separation of the study population in two groups based on baseline AFP levels was discussed. It was pointed out that different cut-off levels of AFP are used in different studies and that the relevance of AFP as clinical surrogate of HCC is not clear. The COMP strongly recommended the sponsor to seek scientific advice in order to address these points in the protocols of the planned Phase III studies.

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

Hepatocellular carcinoma was estimated to be affecting approximately 1 in 10,000 people in the European Union, at the time the application was made. The intention to treat the condition is supported by early clinical data showing favourable time to progression and reduction of biomarkers in patients with refractory/resistant hepatocellular carcinoma. The condition is life-threatening because is often discovered when it is in advanced phase, and survival following diagnosis is approximately 6 to 20 months. The main chronically debilitating manifestations of the condition include abdominal pain, weight loss, ascites, encephalopathy, jaundice and variceal bleeding. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that 4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxamide monohydrate may be of significant benefit to those affected by the condition. This is supported by preliminary clinical data showing favourable time to progression in patients with hepatocellular carcinoma refractory/resistant to currently authorized treatments. This can translate into a clinically relevant advantage as second-line treatment. The favourable outcome in resistant/refractory hepatocellular carcinoma will have to be confirmed at the moment of marketing authorization.

A positive opinion for 4-[2-(6-methylpyridin-2-yl)-5,6-dihydro-4H-pyrrolo[1,2-b]pyrazol-3-yl]-quinoline-6-carboxamide monohydrate, for treatment of hepatocellular carcinoma, was adopted by consensus.

2.1.2 For treatment of glioma - EMA/OD/157/12
[Co-ordinators: K. Kubáčková / S. Mariz]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the medical plausibility. To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of glioma, the sponsor was invited to further elaborate on the relevance and the applicability of the results obtained from the preclinical models used with the sponsors' product for the treatment of glioma.

In the written response, and during an oral explanation before the Committee on 5 February 2013, the sponsor elaborated on the results in the preclinical models and stressed that the concept of immunotherapy was based on a mismatching MHC on glioma tumour cells. It was explained that by analogy, in glioblastoma patients, the product aims to induce an immune reaction thanks to the epitope presentation on mismatching and matching MHC.

The Committee considered that the mechanism of action remains assumptive and not supported by data. In addition it was brought to the attention of the committee that more preliminary clinical data were available, since the product had been administered in several more patients in addition to the two case-studies discussed in the application. These data were not presented by the sponsor and the committee considered that the medical plausibility had not been adequately justified.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 6 February 2013, prior to final opinion.

2.1.3 Gevokizumab for treatment of chronic non-infectious uveitis, Les Laboratoires Servier - EMA/OD/161/12
[Co-ordinators: J. Torrent-Farnell / S. Mariz]

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of chronic non-infectious uveitis, the sponsor was invited to further elaborate on:

- all the studies with the product described in the dossier are designed exclusively in patients with Behçet's disease uveitis. Nonetheless, chronic non-infectious uveitis is associated with a lot of different conditions and not only with Behçet's disease.

- the sponsor was requested to show how the data in Behçet's patients can be extrapolated in uveitis associated with other conditions.

- Prevalence

The sponsor was invited to re-calculate the proposed prevalence of the condition in view of the different subsets that exist under this condition including uveitis associated with Behcets'.

In the written response, and during an oral explanation before the Committee on 5 February 2013, the sponsor further elaborated on the role of IL-1 β in non-infection uveitis. The sponsor discussed that the cytokine has a central role in the inflammatory process associated with chronic non-infectious uveitis and as such the effect of the product in other types of autoimmune uveitis could be similar to that seen in Behcets' disease. The sponsor also provided an updated prevalence calculation as requested, which was revised upwards. After discussion with the sponsor, the COMP accepted that at this stage the

proposed prevalence calculation would be sufficient. The prevalence estimate will be revised at the time of review of the Orphan Medicinal Designation at the time of Marketing Authorization Application.

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

The intention to treat the proposed condition with gevokizumab is considered justified based on preclinical data in animal models and preliminary clinical data showing improved vitreal haze score compared to placebo. Chronic non-infectious uveitis was estimated to be affecting approximately 3.3 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to visual loss. Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that gevokizumab may be of significant benefit to those affected by the condition. This is based on the clinically relevant advantage of improved efficacy, based on preliminary clinical data that show the potential to reduce the loss of visual acuity. A further advantage could be a reduction of corticosteroid use.

A positive opinion for gevokizumab, for treatment of chronic non-infectious uveitis, was adopted by consensus.

2.1.4 Murine IgM monoclonal antibody binding to αβ T-Cell receptor for prevention of graft rejection following solid organ transplant, CTI Clinical Trial and Consulting Services - EMA/OD/165/12
[Co-ordinators: K. Westermark / S. Mariz][Expert: K. Claesson]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the 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 clarify whether the product would be used for the prevention and/or for the treatment of the condition, taking into account the current protocols for the management of acute graft rejection of solid organ transplantation in Europe. In addition the sponsor was invited to clarify whether the product is intended to replace the current regimens or to be used as add-on. In this respect, the sponsor is invited to discuss the clinical added value of using the proposed product in relation to the currently authorized medicinal products, including standard immunosuppressive regimens.

As they refer to literature data using previous similar products, the sponsor should also discuss the potential difference between those products and their product, i.e. if it is possible to extrapolate the results. The sponsor was also invited to discuss the risk of developing antibodies to the product.

In the written response, and during an oral explanation via teleconference on 5 February 2013, the sponsor further discussed the preliminary clinical studies presented in the application and provided the concomitant therapies which were used in their phase II study as requested. In addition, the sponsor stressed that the product is intended as the sole induction agent, replacing either non-depleting agents (such as IL2-R inhibitors, anti-CD3 agents), or depleting agents (such as anti-thymocyte/anti-lymphocyte globulins or anti-CD52). The novel mechanism of action of the product remained in focus in the discussion, with an emphasis on the resulting modulation being short in duration, and recovery of the αβ T cells being observed by day 14 post transplantation.

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

The intention to treat the proposed condition with murine IgM monoclonal antibody binding to alpha beta T-Cell receptor is justified based on preclinical data in animal models and preliminary clinical data

showing improved reduction in graft rejection. The population of patients eligible for prevention of graft rejection following solid organ transplantation was estimated to be affecting not more than 0.9 in 10,000 people in the European Union, at the time the application was made. The condition is life-threatening. Five-year organ transplant success rates currently range from only 37% (intestine) to 80% (kidney). Although satisfactory methods of prevention of the condition have been authorised in the European Union, sufficient justification has been provided that murine IgM monoclonal antibody binding to αβ T-Cell receptor may be of significant benefit to those affected by the condition. This is based on the clinically relevant advantage of improved efficacy, based on preliminary clinical data that show the potential to reduce the risk of graft rejection.

A positive opinion for murine IgM monoclonal antibody binding to alpha beta T-Cell receptor, for prevention of graft rejection following solid organ transplantation, was adopted by consensus.

2.1.5 **Poloxamer 188** for treatment of sickle cell disease, Theradex (Europe) Ltd. - EMA/OD/162/12

[Co-ordinators: L. Gramstad / 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 medical plausibility. To establish correctly if there exists a scientific rationale for the development of the proposed product for the treatment of sickle cell disease, the sponsor was invited to further elaborate on the mechanism of action of the product, and in particular on the events occuring at cell membrane level. The sponsor was also invited to elaborate on possible additional pharmacologic mechanisms of action of the product in the proposed condition, such as e.g. at endothelial level.

In the written response, and during an oral explanation before the Committee on 5 February 2013, the sponsor the sponsor provided additional clarification and description of the mechanism of action and asserted in particular a) the inhibition of red and white blood cells adhesion to endothelium and b) the inhibition of fibrin clot formation by adhesion to fibrin monomers. These actions were considered to be exerted through adherence of Poloxamer 188 on a surface (endothelial layer, fibrin monomers) and mediated by hydrophobic-hydrophobic interaction/adhesion leading to the membrane sealing.

In addition the sponsor produced a number of published papers showing non-physical mechanisms of action of Poloxamer 188. They include a recent article from Hunter et al. (Annals of Clin & Lab Science, 2010) reviewing some of the discovered anti-inflammatory actions of Poloxamer 188 (inhibition of neutrophil chemotaxis *in vitro* and of neutrophil and macrophage accumulation in vivo in bleomycin-challenged rats; multiple effects on oxidative burst and expression of neutrophil adhesion molecules) and describing new experimental data where Poloxamer 188 administered during reperfusion in a superior mesenteric artery occlusion (SMAO) animal model prevented the production of the heme oxygenase mRNA and protein expression induced by the ischemia. Similar effects of Poloxamer 188 were observed by the authors on a variety of genes, including genes for acute phase reactants, interleukins, coagulation factors, chemokines and chemokine receptors, matrix metalloproteinases, aoptosis and VEGF (vascular Endothelial growth factor) among others. In the same paper the authors shed some light on pharmacological effects resulting from the adhesion of Poloxamer 188 to cell membranes, as in the case of sickle red cells. In particular they propose that at least part of the membrane sealing effect promoted by Poloxamer 188 could be related to the inhibition by the product of the cyclooxygenase cascade, through blockage of phospholipase A2 and COX-2.

Poloxamer 188, a copolymer, is part of a group of molecule systems originally known for acting mainly through biophysical mechanisms but for which evidence is being generated of a pharmacological action(s) (see Hitesh and Patel, Int J Pharm Tech Research, 2009). The type and details of such

pharmacological action(s) are explained and demonstrated in a number of published experimental articles. The therapeutic behaviour of Poloxamer 188 in sickle cell disease seems to be linked to different mechanism of actions including biophysical and pharmacological mechanisms, and it is likely that additional mechanisms will be further elucidated in the future as this and similar products are currently undergoing extensive studies. In its clinical translation in sickle cell disease the product seems to act with both mechanical/biophysical and pharmacological mechanisms at three different levels: the sickle red cell, the endothelium, and the formation of the fibrin clot.

The Committee was of the opinion that Poloxamer 188 can be considered a medicinal product for orphan designation based on the above considerations, mainly the existence of a documented pharmacological mechanism of action. Moreover, the importance of pharmacological mechanisms of action in the treatment of sickle cell disease seems plausible when taking into account the repairing effects of the product on the cell membrane.

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

Sickle cell disease was estimated to be affecting less than 1 in 10,000 people in the European Union, at the time the application was made. The intention to treat the condition with the proposed product was supported by preclinical studies showing less rigidity of treated sickle red cells, resulting in improved capillary perfusion and in better survival under hypoxic conditions. The product interacts with the membrane of blood red cells and activates pharmacodynamic effects relevant for the treatment of the disease. In addition preliminary clinical results showed shorter duration of the vaso-occlusive crisis in patients treated with the proposed product. The condition is life-threatening and chronically debilitating due to haemolytic anaemia, and to painful vaso-occlusive crisis with ischemia-reperfusion injury of bone, muscle, or internal organs. This leads to fever, abdominal pain, leg ulcers, aseptic necrosis, and eye damage. Acute chest syndrome may also occur.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that poloxamer 188 may be of significant benefit to those affected by the condition. This appears justified by the clinical data presented by the sponsor, showing reduction of the duration of vaso-occlusive crisis in patients already treated with the currently authorized medicinal product for this condition. The possibility of using the product in combination with the current treatment, and of using it in acute in the vaso-occlusive crisis, represent a potential clinically relevant advantage for the subjects affected by the condition. This will have to be further confirmed prior to marketing authorisation.

A positive opinion for poloxamer 188, for treatment of sickle cell disease, was adopted by consensus.

2.1.6 Recombinant human Heat Shock Protein 70 for treatment of Niemann-Pick disease, type C, Orphazyme ApS - EMA/OD/160/12
[Co-ordinators: P. Evers / 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 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 when used in combination with miglustat or as a monotherapy. The sponsor was requested to further discuss these points by presenting any available data in preclinical models or preliminary clinical settings that support this position.

In the written response, and during an oral explanation before the Committee on 5 February 2013, the sponsor discussed the limitations of the currently authorised treatment and emphasized that

approximately 20% of patients discontinue treatment with miglustat. The sponsor anticipated a clinically relevant advantage stemming from a novel mechanism of action and discussed two studies evaluating rhHSP70 effects in the NPC1$^{-/-}$ mouse model. In particular the effects of administration of rhHSP70 on rearing activity as well as Cat Walk automated gait analysis in NPC1-/- mice are described. In addition, during the oral explanation the sponsor elaborated on the more pronounced effects in this model compared to miglustat, in particular with regards to the effects in weight gain.

The Committee agreed that the condition, Niemann-Pick disease, type C is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing recombinant human heat shock protein 70 was considered justified based on preclinical models which showed that treatment with the product resulted in reduced lysosomal storage of glycolipids and improved motor performance. The condition is chronically debilitating and life-threatening due to neurological degeneration, and hepatosplenomegaly. Niemann-Pick disease, type C was estimated to be affecting approximately 0.1 in 10,000 people in the European Union, at the time the application was made. In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant human heat shock protein 70 may be of significant benefit to those affected by the condition. The proposed product has a novel mechanism of action, interacting with the permeability of the lysosomal membrane, and has exhibited prominent effects in histology and motor performance in a valid preclinical model of the proposed condition. This might suggest a favourable comparison regarding the effects of the authorised counterpart in the same model. Therefore, the potential for improved efficacy was considered plausible. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for recombinant human heat shock protein 70, for treatment of Niemann-Pick disease, type C was adopted by consensus.

2.1.7 For treatment of autosomal dominant polycystic kidney disease - EMA/OD/163/12

[Co-ordinators: A. Corrêa Nunes / 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:

- Description of the condition

The applicant was requested to further discuss why apart from autosomal dominant polycystic kidney disease, autosomal recessive and unspecified forms cannot be part of the proposed indication.

- Medical plausibility

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

- the results from the preclinical models of the proposed condition as applied for;

- the available clinical efficacy studies in the proposed indication as applied for.

- Prevalence

The sponsor was invited to re-calculate the prevalence calculation based on full and not partial prevalence, and given the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor should perform a sensitivity analysis of the reported calculations.

In the written response, and during an oral explanation before the Committee on 5 February 2013, the sponsor elaborated on the differences between the dominant versus the recessive form of the condition, and delineated a different aetiology (the polycystin versus the fibrocystin gene rescpetively) a different pathophysiology (with an emphasis on second hit- mechanisms for the dominant disease) and different clinical characteristics (with the dominant form being a disease of adult with slowly accumulating cysts). As regards the medical plausibility the sponsor discussed the available clinical data showing effects in annual total kidney volume change and clinical progression events including renal function and pain. As per the prevalence calculations the sponsor elaborated on the epidemiological indices used and presented in more details the sources of the calculation.

The Committee considered that one of the main studies used for the calculation, pertains to a study in a French population that gives an overall prevalence that exceeds the provisioned threshold. In addition, the Committee discussed that further epidemiological studies are available for the prevalence of the proposed condition that have not been included in the sponsor's analysis. Therefore, it was considered that the sponsor had not justified that the prevalence criterion was met.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 5 February 2013, prior to final opinion.

2.1.8 Cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L-alpha-glutamyl-L-threonyl] acetat salt for treatment of emphysema secondary to congenital alpha-1 antitrypsin deficiency, Polyphor UK - EMA/OD/166/12

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

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

- Proposed indication

The proposed indication is a subset of congenital alpha-1 antitrypsin deficiency. In line with the updated guideline on the format and content of the applications ENTR6283/00 Rev 03, the restriction of the proposed indication should be justified. The sponsor was invited to broaden the proposed indication to "treatment of congenital alpha-1 antitrypsin deficiency".

- Prevalence

In light of an amended indication, an updated prevalence calculation should be submitted to the Committee.

In the written response the sponsor accepted the proposed revision of the indication and provided an updated prevalence calculation as requested.

Following review of the application by the Committee, it was agreed to rename the indication to "treatment of congenital alpha-1 antitrypsin deficiency".

The Committee agreed that the condition, congenital alpha-1 antitrypsin deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L-alpha-glutamyl-L-threonyl] acetate salt was considered justified based on preclinical models produced by intranasal instillation of neutrophil elastase, which showed that treatment with the product resulted in a reduction of the neutrophil counts and of the concentration of proinflammatory markers in bronchoalveolar lavage. The condition is chronically debilitating and life-threatening due to lung infections and deterioration of lung function. The condition was estimated to be affecting approximately 2.6 in 10,000 people in the European Union, at the time the application was made.

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 cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L-alpha-glutamyl-L-threonyl] acetate salt may be of significant benefit to those affected by the condition. The mechanism of action of the product, which is inhibition of elastase, is complementary to therapy with alpha-1 antitrypsin, and could be expected to be used in combination with the current therapy. In addition, the product will be developed as an inhalation therapy which may not require weekly visits to clinic, as opposed to currently used intravenous therapy.

A positive opinion for cyclo[L-alanyl-L-seryl-L-isoleucyl-L-prolyl-L-prolyl-L-glutaminyl-L-lysyl-L-tyrosyl-D-prolyl-L-prolyl-(2S)-2-aminodecanoyl-L-alpha-glutamyl-L-threonyl] acetate salt, for treatment of congenital alpha-1 antitrypsin deficiency, was adopted by consensus.

2.1.9 **Recombinant adeno-associated viral vector expressing human *retinoschisin* gene** for treatment of X-linked juvenile retinoschisis (XLRS), TMC Pharma Services Ltd - EMA/OD/108/12 [Co-ordinators: A. Magrelli/ K. Westermark / L.Fregonese]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor was asked to clarify the medical plausibility. The sponsor presented literature data on a model and stated that they replicated such data. In order to justify the medical plausibility of the product in the proposed condition the sponsor was invited to provide their own generated proof-of-concept pre-clinical data in the model.

In the written response the sponsor stressed that administration of the rAAV5-hRS1 vector by either the subretinal or intravitreal route in RS1-deficient mice resulted in measurable improvements in ERG a-wave and b-wave amplitude, measured at three months after the administration of the product. The improvement was more evident with intraretinal administration.

The Committee agreed that the condition, X-linked juvenile retinoschisis, is a distinct medical entity and meets the criteria for orphan designation.

X-linked juvenile retinoschisis was estimated to be affecting approximately 0.4 in 10,000 people in the European Union, at the time the application was made. The prevalence was estimated based on relevant literature. The intention to treat the condition with the proposed product is supported by pre-clinical studies showing engraftment of the product in the eye fundus and preservation of photoreceptor structure and function. The condition is chronically debilitating due to the progressive loss of visual acuity which usually starts in the first decade of life and progresses to the so-called “legal blindness” by the sixth or seventh decade. In addition to the slowly progressive loss of visual acuity, patients affected by XLRS are at higher risk of acute events that can lead to worsening of vision, including retinal detachment, vitreous haemorrhage, glaucoma, cataract, and increased formation of

blood vessels in the eye. There is, at present, no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for recombinant adeno-associated viral vector containing the human *retinoschisin* gene, for treatment of X-linked juvenile retinoschisis, was adopted by consensus.

2.2. For discussion / preparation for an opinion

2.2.1 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H- pyrazolo [3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one for treatment of mantle cell lymphoma, Janssen-Cilag International N.V. - EMA/OD/171/12
[Co-ordinators: K. Kubáčková / S. Tsigkos]

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

The intention to treat the condition with the medicinal product containing 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H- pyrazolo [3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one was considered justified based on preliminary clinical studies in Mantle cell lymphoma patients treated with the product, showing objective responses with regards to nodal and extranodal involvement and bone marrow infiltration.

The condition is life-threatening with a median survival of 3 to 5 years and chronically debilitating due to lymphadenopathy, night sweats, fever, and weight loss. The condition was estimated to be affecting approximately 0.17 to 0.56 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 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H- pyrazolo [3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that treatment with the product may induce responses in mantle cell lymphoma patients who were previously refractory or have relapsed following treatment with available satisfactory treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H-pyrazolo [3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one, for treatment of mantle cell lymphoma was adopted by consensus.

2.2.2 For treatment of non-small-cell lung cancer in patients expressing HLA-A2 - EMA/OD/168/12
[Co-ordinators: B. Bloechl-Daum / L. Fregonese]

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

- Orphan indication

The sponsor is invited to justify “non-small-cell lung cancer in patients expressing HLA-A2” as a valid subset having distinct etiologic, histopathologic and clinical characteristics as compared to the broader condition “non-small cell lung cancer”.

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of non-small-cell lung cancer in patients expressing HLA-A2, the sponsor is invited to further elaborate on:

- the specific mechanism of action of the product in the proposed condition

- the methodology and results of the phase I study, where it appears that 6 NSCLC subjects were studied however the immunologic response was evaluated in patients affected by colon cancer. The sponsor is invited to discuss the reasons why the immunologic response of the NSCLC patients is not shown and how the response of colon cancer patients can be extrapolated to NSCLC;

- the use of the immunologic response as proxy of clinical efficacy;

- the lack of response in a number of subjects of this study- what is meant by "*the vaccine was immunogenic and effective at inducing strong and broad CTL responses in a high frequency of patients*". The sponsor is invited to provide figures of such response;

- the methodology and the results of the phase II study on 64 patients, including discussion on the survival figures presented. In this respect, it would be important to know among others, if the survival curves include all patients treated with the proposed product or only the responders. Possible reasons for non-responding should be also addressed.

- Prevalence

The sponsor is invited to re-calculate the provided estimate based on complete prevalence rather than 5-year prevalence.

- Justification of significant benefit

The sponsor is invited to discuss the grounds of significant benefit, including reasoning on why the product would constitute a clinically relevant advantage or major contribution to patient care as compared to what is already authorized for the treatment of the condition. The reasoning should be as much as possible supported by data.

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 March meeting.

2.2.3 **2-[4-Methoxy-3-(2-m-tolyl-ethoxy)-benzoylamino]-indan-2-carboxylic acid** for treatment of systemic sclerosis, Sanofi-Aventis Groupe - EMA/OD/143/12

[Co-ordinators: J. Torrent-Farnell / S. Mariz]

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

The intention to treat the condition with the product was considered justified on the grounds of the pre-clinical data. In these models, treatment with of 2-[4-Methoxy-3-(2-m-tolyl-ethoxy)-benzoylamino]-indan-2-carboxylic acid showed an effect in the condition. Systemic sclerosis was estimated to be affecting less than 3.5 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to the deposition of collagen in the skin and, less commonly, in the kidneys, heart, lungs and stomach. This deposition presents in two forms: diffuse scleroderma which affects the skin as well as the heart, lungs, gastrointestinal tract and kidneys and localized scleroderma which affects the skin of the face, neck, elbows and knees and late in the disease causes isolated pulmonary hypertension. Common complications seen with the diffuse

form are pulmonary hypertension, reflux esophagitis and dysphagia, as well as the appearance of sclerodermal renal crisis. The condition is also life-threatening due to a 5-year survival which has been reported to be decreased. The main causes of mortality in patients with systemic sclerosis are cardiac, interstitial pulmonary disease, pulmonary hypertension, and renal manifestations.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that 2-[4-Methoxy-3-(2-m-tolyl-ethoxy)-benzoylamino]-indan-2-carboxylic acid may be of significant benefit based on the potential effectiveness of the product on the fibrotic process in systemic sclerosis. Based on the pre-clinical data provided, the product is expected to reduce the fibrotic process which is directly associated with the condition and not targeted by the current authorised treatments.

A positive opinion for 2-[4-Methoxy-3-(2-m-tolyl-ethoxy)-benzoylamino]-indan-2-carboxylic acid, for treatment of systemic sclerosis, was adopted by consensus.

2.2.4 For treatment of Glioma - EMA/OD/170/12

[Co-ordinators: B. Bloechl-Daum / 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 particulars of the dose escalating phase I study with regards to the population and the results obtained.

- Justification of significant benefit

The justification of significant benefit is based on a novel mechanism of action that may result in improved efficacy as a clinically relevant advantage compared to authorised products.

The sponsor is requested to further elaborate on the clinical data with regards to any previous treatments received by the respondents, as well as to better quantify the observed responses.

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

2.2.5 For treatment of differentiated thyroid cancer - EMA/OD/173/12

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

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

- Orphan indication

Differentiated thyroid cancer might be perceived as a stage of the disease rather than a distinct medical entity from the perspective of the legal basis of the orphan designation.

Differentiated thyroid cancer should be justified as a distinct medical entity or the application should be split in two separate applications for papillary thyroid cancer and follicular thyroid cancer. The latter is assumed to include also Hürtle cell carcinoma.

- Prevalence

The sponsor is invited to calculate the prevalence according to the possible splitting of the indication into papillary thyroid cancer and follicular thyroid cancer, i.e. providing one prevalence estimate for each of these two conditions.

In addition the sponsor is invited to provide complete prevalence rather than 5-year prevalence of the proposed condition(s), taking into account the duration of the disease.

- Significant benefit

In order to justify the preliminary evidence of a significant benefit, the sponsor is invited to provide more details on the phase II study, in particular regarding the number of patients who were treated, as from the investigator brochure it would appear that 117 subjects were recruited, however only 58 are mentioned in the current application. The number of patients affected by FTC and PTC should also be reported.

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 March meeting.

2.2.6 Mepolizumab for treatment of Churg-Strauss syndrome, Glaxo Group Limited (Greenford) - EMA/OD/174/12
[Co-ordinators: L. Gramstad / L. Fregonese]

The Committee agreed that the condition, Churg-Strauss syndrome, is a distinct medical entity and meets the criteria for orphan designation.

Churg-Strauss syndrome was estimated to be affecting not more than 0.5 in 10,000 people in the European Union, at the time the application was made. The prevalence was estimated based on the available literature on European population. The intention to treat the condition is supported by pre-clinical data, and by early clinical data showing control of the disease in patients treated with mepolizumab. The condition is life-threatening and chronically debilitating due to inflammatory involvement of several organs, in primis the lungs with clinical manifestation of asthma, pulmonary infiltrates, cough and haemoptysis, followed by the heart, the kidneys, the gastrointestinal and the musculoskeletal system. Involvement of the upper airways is characteristic of the disease, and it manifests with allergic rhinitis, paranasal sinusitis and nasal polyposis. The main causes of death are myocarditis and myocardial infarction secondary to coronary arteritis. The 5-year survival rate is 62%. 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 mepolizumab, for treatment of Churg-Strauss syndrome, was adopted by consensus.

2.2.7 For treatment of neuroendocrine tumours - EMA/OD/185/12
[Co-ordinators: B. Dembowska-Bagińska / S. Mariz]

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

- Medical plausibility

The sponsor has proposed that bibliographical data where other types of therapies have been used support the use of their product for treatment of neuroendocrine tumours. The sponsor has not presented any data that they may have generated on their own with their product in the proposed condition. The sponsor is therefore invited to further elaborate on the relevance of using the proposed bibliographical data to support the medical plausibility.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation. The sponsor should indicate on which population the prevalence calculation is based on. In this case the COMP would need to see all forms of neuroendocrine tumours as currently defined in current publications. The sponsor is invited to re-calculate the prevalence calculation based on relevant epidemiological studies and registries for the proposed orphan condition in this case is neuroendocrine tumours.

- 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. This is based on extrapolation from bibliographical data with other therapies. The sponsor has not submitted any data of their own which would support the significant benefit with the current therapeutic algorithms and comparison to currently approved therapies in this condition. The sponsor should further elaborate on this.

- Development of Medicinal Product

The sponsor should clarify if the product applied for will be developed, and provide detailed information and update the Committee on the current stage of development of the product.

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 March meeting.

2.2.8 For diagnosis of neuroendocrine tumours - EMA/OD/181/12

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

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

- Medical plausibility

The sponsor has based their medical plausibility for the proposed product for the diagnosis of neuroendocrine tumours on a hypothesis but has not supported this with any data of their own or bibliographical data. The sponsor is invited to present supporting data either non-clinical and/or, if available clinical data with their product showing the plausibility of using it in the diagnosis of neuroendocrine tumours.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation. The sponsor should indicate on which population the prevalence calculation is based on. In this case the COMP would need to see all forms of neuroendocrine tumours as currently defined in current publications. The sponsor is invited to re-calculate the prevalence calculation based on relevant epidemiological studies and registries for the proposed orphan condition in this case the diagnosis of neuroendocrine tumours.

- Justification of significant benefit

The sponsor has not established the significant benefit of using the product, a diagnostic for neuroendocrine tumours over OctreoScan which is a kit for radiopharmaceutical preparation of ^{111}In-Pentetreotide and is approved in Europe for this purpose. The sponsor is invited to further elaborate on the sensitivity and specificity of the product over the currently approved diagnostic methods in Europe.

- Development of Medicinal Products

The sponsor should clarify if the product applied for will be developed, and provide detailed information and update the Committee on the current stage of development of the product.

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 March meeting.

2.2.9 For treatment of osteonecrosis of the femoral head - EMA/OD/176/12
[Co-ordinators: K. Westermark / L. Fregonese]

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

- Medical plausibility

Osteonecrosis of the femoral head should be justified as a distinct medical entity or a valid subset or the application should be changed accordingly. The sponsor is invited to justify the restriction of the use of the product in osteonecrosis of the femoral head. This should not be based on a potential envisioned therapeutic indication but on the definition of a subset (distinct etiologic, histopathologic and clinical characteristics as compared to the broader condition, in this case osteonecrosis). Thus the sponsor should justify why the product would not work outside the proposed subset of osteonecrosis of the femoral head.

- Prevalence

The sponsor should recalculate the prevalence according to the revised condition

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

2.2.10 Ramiprilat for treatment of Stargardt's disease, Iris Pharma - EMA/OD/175/12
[Co-ordinators: J. Torrent-Farnell/ A. Lorence / S. Mariz]

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

The intention to treat the proposed condition with ramiprilat is considered justified based on preclinical data in animal models and preliminary clinical data showing improved vitreal haze score compared to placebo. Stargardt's disease was estimated to be affecting approximately 1.2 in 10,000 people in the European Union, at the time the application was made. The condition is chronically debilitating due to significant loss in central vision with a marked reduction in visual acuity in their first or second decade of life. There is, at present, no satisfactory method of treatment that has been authorised in the European Union for patients affected by the condition.

A positive opinion for ramiprilat, for treatment of Stargardt's disease, was adopted by consensus.

2.2.11 Recombinant human TriPeptidyl-Peptidase 1 for treatment of Neuronal Ceroid Lipofuscinosis type 2 (NCL2), BioMarin Europe Ltd. - EMA/OD/177/12
[Co-ordinators: J. Torrent-Farnell / S. Mariz]

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

The intention to treat the condition with the product was considered justified on the grounds of the pre-clinical data. In this model, treatment with Recombinant human TriPeptidyl-Peptidase showed an effect in the condition. Neuronal ceroid lipofuscinosis type 2 was estimated to be affecting approximately 0.3 in 10,000 people in the European Union, at the time the application was made. A literature search was carried out to establish the prevalence in Europe. The condition is chronically debilitating due to a progressive degeneration of the brain and retina. The hallmarks of the disease are progressive degeneration of the brain and retina mediated by apoptosis of neurons and photoreceptors. It begins between ages 2 and 4 years. The typical early signs are loss of muscle coordination (ataxia) and seizures along with progressive mental deterioration, though afflicted children may show mild-severe delays in speech development well before other symptoms appear. It is life-threatening as it progresses rapidly and ends in death between ages 8 and 12. 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 tripeptidyl-peptidase 1, for treatment of neuronal ceroid lipofuscinosis type 2, was adopted by consensus.

2.2.12 For treatment of chronic inflammatory demyelinating polyneuropathy - EMA/OD/169/12
[Co-ordinators: H. Metz / 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 the treatment of the proposed condition, the sponsor should further elaborate on the relevance of the in vitro model used for the treatment of chronic inflammatory demyelinating polyneuropathy, and the interpretation of the results obtained in the experiments.

In particular the sponsor has shown that the proposed product abrogates MRSV Env-induced CXCL10 expression in Schwann cell cultures. The sponsor is requested to discuss any further available data in relevant models of CIDP or in preliminary clinical settings.

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy, safety and major contribution to patient care in the condition. 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 March meeting.

2.2.13 For treatment of pancreatic cancer - EMA/OD/178/12
[Co-ordinators: B. Bloechl-Daum / S. Tsigkos]

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

- Medical plausibility

To establish if there is medical plausibility to treat the condition with the proposed product, the sponsor is invited to further elaborate on:

- the results from the preclinical studies presented in the application

- any available data that support that the product as proposed for designation might elicit an immune response against its target

- any available data that support that the product might elicit anti-angiogenic responses in relevant models or preliminary clinical settings

- any available data in preclinical and/or clinical settings that might show effects in tumour control.

- Justification of significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy and improved safety in the condition. The sponsor should detail the results of any data they have to support these two points.

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 March meeting.

2.2.14 For treatment of *Pseudomonas aeruginosa* infection in cystic fibrosis - EMA/OD/179/12
[Co-ordinators: J. Eggenhofer / L. Fregonese]

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

- Medical plausibility

In order to establish the medical plausibility of treating the proposed condition with the proposed product, the sponsor is invited to further discuss the extrapolation of the in vitro results on biofilms to the clinical manifestations of CF.

- Prevalence

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

- Justification of significant benefit

The sponsor mentions three potential advantages that would support the significant benefit of the product: synergistic effect of the combination (based on the in vitro data), anti-inflammatory effects, and optimised drug delivery system.

The first two advantages can also be achieved by oral co-administration of clarithromycin with inhaled tobramycin. In this respect, the sponsor is invited to elaborate on the advantages of administering the two products in a fixed combination rather than separately, taking into account:

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

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

- the possibility of increasing broad spectrum antibiotic resistances

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

The sponsor will be invited to an oral explanation before the Committee at the March meeting.

Post-meeting note:

The list of issues was adopted by the COMP via written procedure on 13 February 2013.

2.2.15 For treatment of epidermolysis bullosa - EMA/OD/180/12
[Co-ordinators: D. Krievins / S. Tsigkos]

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

- Medical plausibility

The proposed mechanism is described in generic terms. None of these claims with regards to the mechanism of action is either specified or supported by any data presented in the application. Whatever more, the sponsor asserts that the product "…has no pharmacological effect in itself". Therefore the proposed mechanism of action remains at least assumptive. The sponsor is invited to further elaborate whether the proposed product has a mechanical or pharmacological effect mode of action.

In addition, the sponsor is invited to further elaborate on:

- the proposed mechanism of action based on data in relevant models

- any further available data to support the proof of concept in either preclinical models or preliminary clinical settings.

- Prevalence

The sponsor should justify the sources of the prevalence data and describe the methodology used for the prevalence calculation. A clear overall conclusion is expected for the time the application is made.

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 March meeting.

2.3. Appeal procedure

2.3.1 Zoledronic acid for treatment of complex regional pain syndrome, Axsome Therapeutics Limited - EMA/OD/125/12
[Co-ordinators: K. Westermark / S. Tsigkos]

Following the COMP negative opinion adopted on 6 December 2012, the sponsor submitted the grounds for appeal on 21 January 2013.

In the grounds, and during an oral explanation before the Committee on 6 February 2013, the sponsor discussed again the proposed pharmacological properties of zoledronic acid and other biophosphonates, spanning anti-inflammatory, anti-osteoclastic, and direct analgesic effects based on literature studies. These pharmacodynamic effects were considered to be relevant for the treatment of the condition, based on its clinical features and in particular pain. The sponsor also re-discussed published randomised controlled clinical trials with other bisphosphonates in patients with the proposed condition, and based on the results from these studies and from other published literature, proposed a class effect of bisphosphonates in the treatment of CRPS. Moreover, the sponsor presented arguments to justify the validity of the abstract by Zaspel et al, including reviewers' opinions, as well as expert opinions on the medical plausibility argument. The full study report from the cited abstract was not presented to the Committee.

In the subsequent discussion, the COMP explained to the sponsor that a designation is given to a specific product in relation to a specific proposed indication, and that so far the sponsor has not presented data with the proposed product to justify the intention to treat the condition as applied for. Of all the arguments presented in the appeal, the most direct data pertained to a non-sponsor generated abstract with a different medicinal product containing zoledronic acid (Zaspel et al, 2007) which was not considered sufficient because the particulars of the study were not available for evaluation. In particular there is no data on important methodological aspects of the study that would affect the interpretation of the results, such as the randomisation to the experimental groups or any measures to conceal allocation. In addition the results on pain are presented as a relative value but there is no data about baseline values. Moreover the analysis of data is not described. All these elements affect negatively the possibility to draw valid conclusions from the data presented.

The Committee considered as follows:

- complex regional pain syndrome 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 prevalence estimate was based on relevant international literature.
- the condition is chronically debilitating in those cases which do not undergo spontaneous resolution. In those cases, the chronically debilitating nature of the disease is due to symptoms such as pain, oedema, motor, sensorial, and vasomotor disturbances in the affected region. Continuous disabling pain has been described as the hallmark of the disease; it is disproportionate to the inciting event and lasts beyond the healing period. As the disease progresses, the pain often spreads beyond the affected limb. Autonomic symptoms and motor dysfunction can develop, including dystonia, tremor, myoclonus and muscle weakness.
- the sponsor has demonstrated that there exists no satisfactory method of treatment of the condition in question that has been authorised in the European Union.
- the intention to treat the condition with the above-mentioned product has been considered by the Committee not to be justified by the sponsor. The Committee was of the opinion that the sponsor did not provide sufficient data to support the potential clinical use of the product in complex regional pain syndrome. The most direct data presented by the sponsor, pertained to a non-sponsor generated abstract with a different medicinal product containing zoledronic acid (Zaspel et al, 2007) which was not considered sufficient because the particulars of the study were not available for evaluation. The sponsor did not present any data with the proposed route of administration as applied for designation.

The Committee has therefore concluded that the sponsor has not established that the product is intended for the treatment of the proposed condition.

A final negative opinion for zoledronic acid, for treatment of complex regional pain syndrome, was adopted by consensus.

2.4. Evaluation on-going

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

2.5. Validation on-going

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

3. Requests for protocol assistance

3.1 For treatment of granulomatosis with polyangiitis (Wegener Granulomatosis) [Coordinator: R. Elbers]

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

4. Overview of applications

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

COMP co-ordinators were appointed for 1 application submitted and 23 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 Bosulif (Bosutinib) for treatment of chronic myeloid leukaemia; Pfizer Limited (OD/160/09, EU/3/10/762)
[Co-ordinators: K. Kubackova / S. Tsigkos]

The CHMP opinion on marketing authorisation was adopted in January 2013.

The COMP concluded that:

The proposed therapeutic indication “Bosulif is indicated for the treatment of adult patients with chronic phase (CP), accelerated phase (AP), and blast phase (BP) Philadelphia chromosome positive chronic myelogenous leukaemia (Ph+ CML) previously treated with one or more tyrosine kinase inhibitor(s) and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options“, falls entirely within the scope of the orphan indication: “treatment of chronic myeloid leukaemia”.

The prevalence of chronic myeloid leukaemia was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria, and affecting approximately 1 in 10,000 people in the EU. The condition is chronically debilitating and life threatening due to the consequences of the bone marrow dysfunction, such as intracranial or gastro-intestinal haemorrhagic episodes, disseminated

intravascular coagulation, and the risk of severe infections. The condition progresses rapidly and is fatal within days to weeks or a few months if left untreated. The overall 5-year relative survival with the currently available treatments is approximately 22%.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Bosulif (Bosutinib) may be of potential significant benefit to those affected by the orphan condition still holds. This was considered justified on the grounds of the clinically relevant advantage of providing an alternative in a niche population with limited or no other treatment options. This was based on documented clinical responses in a population of adult Philadelphia chromosome positive chronic myeloid leukaemia patients, for whom treatment with other tyrosine kinase inhibitors was not considered appropriate.

Post-meeting note:

An opinion not recommending the removal of Bosulif (Bosutinib) (EU/3/10/762) from the EC Register of Orphan Medicinal Products and the draft public summary of the COMP opinion were adopted by consensus via written procedure on 13 February 2013.

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

5.2.1 Pheburane (Sodium phenylbutyrate) for treatment of carbamoyl-phosphate synthase-1 deficiency; Lucane Pharma SA (EU/3/12/951)

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. (EU/3/05/314)

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 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)

5.3.4 Cysteamine bitartrate [Cysteamine bitartrate (gastroresistant)] for treatment of cystinosis; Raptor Pharmaceuticals Europe B.V. (EU/3/10/778)

5.3.5 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)

5.3.6 Delamanid ((R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole) for treatment of tuberculosis; Otsuka Novel Products GmbH (EU/3/07/524)

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

5.3.8 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 (EU/3/02/092)
Type II variation – for treatment of chronic iron overload due to blood transfusions in patients with beta thalassaemia major aged 6 years and older.

5.3.9 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)

5.3.10 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

- treatment of chronic myeloid leukaemia (EU/3/09/716)
- treatment of acute lymphoblastic leukaemia (EU/3/09/715)

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

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

5.3.13 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)

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

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

5.3.16 Pomalidomide Celgene (Pomalidomide) for treatment of multiple myeloma; Celgene Europe Ltd. (EU/3/09/672)

5.3.17 Revlimid (3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione) for treatment of myelodysplastic syndromes; Celgene Europe Limited – UK (EU/3/04/192)
Type II variation - for treatment of patients with transfusion-dependent anaemia due to low- or intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities.

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

5.3.19 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)

5.3.20 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)

5.3.21 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)

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

6. Procedural aspects

6.1 Appointment of the 3rd COMP representative to the EMA Scientific Advice Working Party (SAWP)

The COMP nominated A. Magrelli as their 3rd COMP representative in the SAWP.

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

The Committee noted the PCWP meetings documents.

7. Any other business

7.1 COMP Informal meeting held on 22-23 November 2012 in Rome

The Minutes of the meeting were adopted.

7.2 COMP Informal meeting to be held on 28 February - 1 March 2013 in Dublin

The draft Agenda for the meeting was presented and adopted.

7.3 COMP Work Programme 2013-2015

The topic was postponed.

Date of next COMP meeting: 12 - 13 March 2013

List of participants

Chair:

Bruno Sepodes

COMP Members:

André Lhoir	België/Belgique/Belgien
Irena Bradinova	България
Kateřina Kubáčková	Česká Republika
Dorthe Meyer	Danmark
Vacant	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
Aušra Matulevičienė	Lietuva
Judit Eggenhofer	Magyarország
Albert Vincenti	Malta
Violeta Stoyanova-Beninska	Nederland
Bożenna Dembowska-Bagińska	Polska
Ana Corrêa-Nunes	Portugal
Vacant	Slovensko
Veijo Saano	Suomi/Finland
Kerstin Westermark	Sverige
Daniel O'Connor	United Kingdom
Birthe Byskov Holm	Volunteer patient representative for Eurordis
János Borvendég	CHMP Representative
Aikaterini Moraiti	CHMP Representative
Vacant	EMA Representative

Observers:

Maria Mavris	Eurordis
Vesna Osrecki	Croatia

European Commission:

Agnès Mathieu	DG Health and Consumers

EMA:

Jordi Llinares Garcia	Head of Orphan Medicines
Stiina Aarum	Scientific Administrator (present on 1st day only)
Laura Fregonese	Scientific Administrator (present on 2nd day only)
Segundo Mariz	Scientific Administrator
Stylianos Tsigkos	Scientific Administrator
Federica Castellani	Scientific Administrator (for 5.1.1 only)
Agnieszka Wilk-Kachlicka	Assistant
Frederique Dubois	Assistant

Apologies

Vice-Chair:

Lesley Greene	Volunteer patient representative for Eurordis

Members:

Dainis Krievins	Latvija
Henri Metz	Luxembourg
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Österreich
Flavia Saleh	Romãnia
Martin Možina	Slovenija
Pauline Evers	Patient representative representing the European Genetic Alliances Network

Observers:

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