EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

5 October 2012
EMA/COMP/471400/2012
Human Medicines Development and Evaluation

Committee for Orphan Medicinal Products (COMP)

Minutes of the 4-5 September 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/COMP471398/2012

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the COMP meeting held on 10-11 July 2012, EMA/COMP/404711/2012

The COMP was informed that the final minutes of the COMP meeting will be published on the EMA web site. The draft document was circulated for discussion. Following comments from the members it was decided to circulate the final minutes again in the post-mailing.

1.3 Conflicts of Interest

The COMP secretariat was informed as follows:

- Eurordis receives funding from the sponsor who have submitted dossier to be considered for orphan designation at the current meeting (2.2.10). 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 sponsors for applications under agenda point 2.1.9 and 2.2.12. Nevertheless, no direct conflicts of interest have been identified for P. Evers, who is representing EGAN in the COMP.

1.4 Election of Chair and Vice-Chair

The COMP noted the following candidates:

- R. Elbers, candidate for the Chair
- B. Sepodes, candidate for the Chair
- L. Greene, candidate for the Vice-Chair

The motivation letter and CVs of the candidates were circulated in the pre-mailing. The COMP Rules of procedure EMA/COMP/8212/00 Rev. 3 were also circulated and the Committee was briefed on the rules governing the elections for the COMP Chair and Vice-Chair.

B. Sepodes was elected chair by simple majority in the third round. L. Greene was voted the Vice-Chair by majority in the first round.

The votes were counted and recorded by two tellers from the Agency nominated for the occasion.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Asp-Arg-Val-Try-Ile-His-Pro for treatment of acute lung injury, Tarix Pharmaceuticals Limited - EMA/OD/062/12
[Co-ordinators: M. Možina / L. Fregonese]

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

To establish correctly if there exists a scientific rationale for the development of the product for the treatment of acute lung injury, the sponsor was invited to clarify whether the studies presented for supporting the medical plausibility are sponsor-generated or are literature studies.

In the latter case, the sponsor was invited to discuss how the sponsor's product relates to the products used in the published studies. In addition the sponsor was invited to discuss the relevance of the preclinical studies.

In relation to the aforementioned studies, the sponsor was invited to further discuss the possible mechanism of action of the product in the observed responses in ALI.

The sponsor presented several studies related to fibrosis in models. The sponsor was invited to clarify the relevance of the anti-fibrotic activity to the proposed condition.

The sponsor was also invited to further describe the development of the product in the proposed condition, including some more extended discussion on the planned clinical studies (e.g. planned protocol and feasibility).

In the written answers and the oral explanation the sponsor adequately answered to the concerns raised by the COMP in the List of Questions. The relationship between the mechanism of action of the medicine and the development of ALI was clarified.

The relevance of the preclinical models was clarified and an additional model was discussed. The models and endpoints were acknowledged by the Committee.

The role of fibrosis in the pathogenesis of ALI in relation to the proposed product and its mechanism of action was briefly discussed. At the present stage of the development of the product the Committee could not envision the use of the product in the fibrotic stages of ALI, but such use is worth being addressed in the future development.

The Committee expressed a positive opinion on the orphan designation.

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

Acute lung injury was estimated to be affecting not more than 3.4 in 10,000 people in the European Union, at the time the application was made. The sponsor based the calculations on the evaluation of valid sources, including a vast literature search, and databases.

The condition is life-threatening, with mortality rates of approximately 40-60%. It is characterised by widespread damage to cells and structures of the alveolar capillary membrane which occurs within

[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).

hours to days of a predisposing insult. Irreversible respiratory failure is the cause of death in less than 10% of ALI patients. After the first three days of ALI, most deaths are a consequence of multiple organ system failure and/or sepsis. Frequently occurring complications include baro- and volutrauma, pulmonary hypertension, pneumothorax and bacterial infections. Abnormal organ function in addition to lung failure caused by ALI can develop and may involve the liver, kidney, brain, blood or immune system.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that Asp-Arg-Val-Try-Ile-His-Pro 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 new mechanism of action. The assumption for a potential benefit is supported by preclinical data in two models, where parameters of relevance for the treatment of ALI (e.g. pulmonary oedema) were improved by treatment with Asp-Arg-Val-Try-Ile-His-Pro.

A positive opinion for Asp-Arg-Val-Try-Ile-His-Pro, for treatment of acute lung injury, was adopted by consensus.

2.1.2 For treatment of cystic fibrosis - EMA/OD/052/12

[Co-ordinators: J. Eggenhofer / S. Tsigkos]

As agreed during the July 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 proposed product for cystic fibrosis, the sponsor is invited to further elaborate on the relevance of the preliminary clinical data with the product as proposed in single dose studies in non-cystic fibrosis (CF) bronchiectasis patients for the treatment of CF.

- Justification of significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit by commenting on specific data obtained with the proposed product subject of this application. The sponsor was asked also discuss the clinical advantages compared to other equivalent inhalation products in the treatment of CF.

In its written response, and during an oral explanation before the Committee on 4 September 2012, the sponsor focused on safety concerns as the grounds to support significant benefit. In view of the small number of patients exposed to the combination proposed it was felt that at this stage in development safety argumentation was insufficient to satisfy the requirements to establish significant benefit.

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

2.1.3 For treatment of sarcoidosis, - EMA/OD/044/12

[Co-ordinators: B. Sepodes/ J. Eggenhofer / S. Tsigkos]

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

2.1.4 For treatment of opioid overdose, - EMA/OD/067/12
[Co-ordinators: L. Gramstad / L. Fregonese]

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

- Medical plausibility

It appears unclear to what extent the product is developed into a medicinal product for intranasal administration. As yet the pharmaceutical formulation as well as the nasal spray device is briefly described in prospected terms. The sponsor was invited to provide a description of the medicinal product as developed at this stage. The sponsor was asked also to explain how data in the literature can be extrapolated to their coming product, since the strength of the planned formulation is much higher than reported in the published references.

- Prevalence

The sponsor was invited to clarify how "opioid overdose" in the sought condition is defined as reported in the provided statistical data. The data used from EMCDDA seems to include overdoses primarily linked to illicit opioids. Since occurrences of opioid overdose have become an increasing concern in pain therapies, the sponsor was asked to present available data and to discuss to what extent opioid overdose in this population will influence the overall prevalence estimate.

- Justification of significant benefit

The sponsor claims significant benefit based on the development of a formulation for intranasal use. However, as already said such formulation has not yet been completely developed. The sponsor was asked to better clarify the impact of the intranasal formulation on the treatment of opioid overdose.

In its written response, and during an oral explanation before the Committee on 4 September 2012, the sponsor discussed the state of development of the product formulation and the issues related to prevalence as asked by the COMP. The discussion was mainly focused on the incidence of opioid overdose in Europe. The sponsor provided an exhaustive overview of the current epidemiology of opioid overdose and consulted a large range of valid sources of the incidence of opioid overdose. However the Committee argued that any currently available estimate of mortality would not reflect all potential opioid overdoses in Europe. EMCDDA reports state that mortality from opioid use is probably under-reported in Europe. The COMP discussed the fact that opioid overdoses not reaching hospital should be accounted for in the calculation of the population which would benefit from intranasal treatment. For all these reasons the COMP considered that the population eligible for treatment with the proposed product would not fall within the prevalence threshold of orphan designation.

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

2.1.5 **Rucaparib** for treatment of ovarian cancer, Clovis Oncology UK Limited - EMA/OD/085/12
[Co-ordinators: B. Bloechl-Daum / S. Mariz]

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

- Medical plausibility

In the application, the sponsor provides non-clinical data in tumour models, including ovarian cancer, to support the effect of the product.

These data show that of the tumours tested, ovarian cancer is the one showing one of the most modest responses to the product. The sponsor was asked to elaborate on this finding also in relation to the clinical data, which indicates that only partial and stable disease have been reported in ovarian cancer.

- Justification of significant benefit

Patients with ovarian, primary peritoneal, or fallopian tube cancer have been included in trials with the medicinal product. Partial responses and stable disease have been observed. The sponsor was requested to provide updated results and to elaborate on the justification for significant benefit, including a critical discussion of the background treatments of the patients showing response and the effect versus homologous recombination status.

In its written response, and during an oral explanation before the Committee on 4 September 2012, the sponsor presented additional data from an independent study where their product was used. This additional data provided sufficient evidence to adequately answer the question raised by the COMP.

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 2.1 in 10,000 people in the European Union, at the time the application was made; this was based on data derived from Globocan and Eurocare.

The sponsor has provided satisfactory argumentation to establish that the condition is chronically debilitating, in particular due to abdominal pain or discomfort, an abdominal mass, bloating, back pain, urinary urgency, constipation, tiredness and a range of other non-specific symptoms, as well as more specific symptoms such as pelvic pain, abnormal vaginal bleeding or involuntary weight loss. There can be a build-up of fluid (ascites) in the abdominal cavity. The life threatening nature of the condition is associated with the fact that most patients with ovarian cancer have widespread disease at presentation. This may be partly explained by the relatively early spread of high grade papillary serous cancers to the rest of the peritoneal cavity. Five year survival in Europe has been estimated to be 40%.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that rucaparib 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 preliminary clinical data where patients with the BRCA mutation as well as patients who are platinum resistant have shown clinical response.

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

2.1.6 For treatment of pancreatic cancer, - EMA/OD/068/12
[Co-ordinators: B. Bloechl-Daum / S. Tsigkos]

As agreed during the July 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 that a scientific rationale exists for the proposed condition as applied for, the sponsor was requested to provide the results and discuss in detail the phase I clinical study discussed in the medical plausibility section.

- Significant Benefit

The sponsor was requested to further elaborate on the justification of significant benefit based on the detailed results and further particulars of the above mentioned phase I clinical study.

In its written response, and during an oral explanation before the Committee on 4 September 2012, the sponsor discussed the available data from the phase I study. Such data were considered by the COMP not sufficient to justify the significant benefit of the product in relation to the currently existing treatments. Clinical results in more advanced study phases would be needed for assuming a possible significant benefit of the product.

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

2.1.7 For treatment of patients with Coenzyme Q10 primary deficiency syndrome, - EMA/OD/057/12 *[Co-ordinators: R. Elbers/ L. Greene / S. Tsigkos]*

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

2.1.8 [2-cyano-3-cyclopropyl-3-hydroxy-N-(3-methyl-4-trifluoromethylphenyl)prop-2-enamide] for treatment of spinal cord injury, Algiax Pharmaceuticals GmbH - EMA/OD/088/12 *[Co-ordinators: H. Metz / S. Tsigkos]*

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

- Proposed condition

The sponsor was invited to amend the proposed indication to "treatment of traumatic spinal cord injury".

- Prevalence

The sponsor was invited to recalculate the prevalence of traumatic spinal cord injury taking into account the duration of the condition.

In its written response the sponsor adequately re-calculated the prevalence according to the revised condition "treatment of traumatic spinal cord injury" and the duration of the condition.

Following review of the application by the Committee, it was agreed to rename the indication to "treatment of traumatic spinal cord injury".

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

Traumatic spinal cord injury was estimated to be affecting approximately 3 in 10,000 people in the European Union, at the time the application was made.

The condition is chronically debilitating due to serious motor deficits that can affect all limbs, sensory deficits, neuropathic pain, venous thromboembolism, development of pressure ulcers, heterotopic ossification, neurogenic bladder, and neurogenic bowel. The condition is also life-threatening with approximately half of the patients dying in the first month after injury.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that [2-Cyano-3-cyclopropyl-3-hydroxy-N-(3-methyl-4-trifluoromethylphenyl)prop-2-enamide may be of significant benefit to those affected by the condition. This is based on a potential clinically relevant advantage supported by preclinical results showing significant attenuation of the establishment of motor deficits following traumatic spinal cord injury in rodents treated with [2-Cyano-3-cyclopropyl-3-hydroxy-N-(3-methyl-4-trifluoromethylphenyl)prop-2-enamide]. The same study also showed significant recovery of neurosensorial function even when the product is administered at three months post injury.

A positive opinion for [2-Cyano-3-cyclopropyl-3-hydroxy-N-(3-methyl-4-trifluoromethylphenyl)prop-2-enamide], for treatment of traumatic spinal cord injury, was adopted by consensus.

2.1.9 **Mavoglurant** for treatment of Fragile X Syndrome., Novartis Europharm Limited - EMA/OD/059/12

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

As agreed during the July meeting, a list of issues was sent to the sponsor for written response. The sponsor was invited to re-calculate the prevalence calculation based on relevant epidemiological studies and registries for the proposed orphan condition, and given the substantial uncertainty about the assumptions regarding the prevalence, the sponsor was asked to perform a sensitivity analysis of the reported calculations.

In its written response the sponsor adequately re-calculated the prevalence as requested by the COMP.

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

Fragile X syndrome was estimated to be affecting approximately 2 in 10,000 people in the European Union, at the time the application was made.

The condition is chronically debilitating in particular due to neurobehavioral and neurodevelopmental symptoms including cognitive impairment, anxiety, irritability, social withdrawal, inattention and hyperactivity. Autism spectrum disorder presentation could be some of the behavioural symptoms exhibited by affected individuals, and approximately one third of patients with the condition meet clinical criteria for autism spectrum disorders. Epileptic seizures occur in about 20% of patients.

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 mavoglurant, for treatment of fragile X syndrome, was adopted by consensus.

2.2. For discussion / preparation for an opinion

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

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

- Prevalence

The sponsor is 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 is 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.

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 October meeting.

2.2.2 Mixture of two allogeneic human pancreatic cancer cell lines stably transduced with a retroviral vector encoding the murine *alpha-(1,3)-galactosyltransferase* gene for treatment of pancreatic cancer, European Medical Advisory Services Limited - EMA/OD/065/12
[Co-ordinators: D. O'Connor / S. Mariz]

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

Pancreatic cancer was estimated to be affecting approximately 1.3 in 10,000 people in the European Union, at the time the application was made; the sponsor has based this on the Globocan database. The sponsor has established that the condition is chronically debilitating and life threatening due to a poor prognosis, partly because the cancer usually causes no symptoms early on, leading to locally advanced or metastatic disease at time of diagnosis. It can be associated with pain and pain in the upper abdomen, loss of appetite and/or nausea and vomiting and weight loss. Jaundice occurs when a cancer of the head of the pancreas (75% of cases) obstructs the common bile duct. The jaundice may be associated with itching as the salt from excess bile can cause skin irritation. It may occasionally cause the appearance of diabetes where insulin production is hampered. Fatigue, weakness and depression are also often noted. Survival at one year in patients diagnosed with pancreatic cancer has been estimated to be 20%.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that mixture of two allogeneic human pancreatic cancer cell lines stably transduced with a retroviral vector encoding the murine *alpha-(1,3)-galactosyltransferase* gene may be of significant benefit to those affected by the condition. This is based on the clinically relevant advantage of improved efficacy, on the grounds of an alternative mechanism of action that may allow for an add-on use with the currently authorised methods of treatment. This is supported be preliminary clinical data showing improved survival rate when the product is combined with the current standard of care.

A positive opinion for mixture of two allogeneic human pancreatic cancer cell lines stably transduced with a retroviral vector encoding the murine *alpha-(1,3)-galactosyltransferase* gene, for treatment of pancreatic cancer, was adopted by consensus.

2.2.3 Alpha-1 proteinase inhibitor (for inhalation use) for treatment of cystic fibrosis, Grifols Deutschland GmbH - EMA/OD/058/12
[Co-ordinators: J. Eggenhofer/ V. Stoyanova / S. Mariz]

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

Cystic fibrosis was estimated to be affecting approximately 0.7 in 10,000 people in the European Union; the sponsor based the calculations on the evaluation of valid sources, including a vast literature search, and on databases.

The condition is life-threatening and chronically debilitating due to the repeated and antibiotic-resistant respiratory infections and the development of bronchiectasis. Death can occur from terminal respiratory failure or erosion of the large pulmonary vessels by the destructive processes which accompany the respiratory infections. The exocrine pancreatic enzyme deficiency is not lethal but adds to the chronic debilitation induced by the disease due to malabsorption and malnutrition.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that alpha-1 proteinase inhibitor (for inhalation use) may be of significant benefit to those affected by the condition. This appears justified in particular with regards to a potential clinically relevant advantage due to a different mode of action which acts on elastase activity. This is supported by preliminary clinical data in patients with cystic fibrosis.

Due to the lack of quorum the COMP opinion for alpha-1 proteinase inhibitor (for inhalation use), for treatment of cystic fibrosis will be adopted via written procedure.

Post-meeting note:

The draft Summary Report with the grounds for a positive opinion was circulated on 7 September and adopted by the COMP on 12 September.

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

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

- Medical plausibility

To establish correctly if there exists a scientific rationale for the development of the product for treatment of Friedreich's ataxia, the sponsor is invited to further elaborate on:

- the pharmacodynamics and functional connection between a vitamin E derivative and Friedrich's ataxia which seems to be caused by expanded GAA triplet repeat on an intron of a nuclear frataxin gene compromising the function of a mitochondrial protein involved in the management of Fe-S cluster;

- the clinical data of the phase II study;

- the negative results obtained up to date with other antioxidants used in this condition.

- Prevalence

The sponsor did not present a final estimate of the prevalence of Friedrich's ataxia in the EU. The sponsor is invited to present such estimate.

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 October meeting.

2.2.5 Belinostat for treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukemic/disseminated), TopoTarget A/S - EMA/OD/103/12
[Co-ordinators: D. O'Connor / S. Tsigkos]

The Committee agreed that the condition, peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated), is a distinct medical entity and meets the criteria for orphan designation.

Peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated was estimated to be affecting less than 1 in 10,000 people in the European Union when the application was made.

The condition is chronically debilitating and life-threatening due to poor response to therapy and high rate of relapses. Five year overall survival is reported at average 25% to 40%, depending on sub-type, with most relapses occurring within 12 months. Clinical presentation and course vary from an indolent clinical behaviour for years in milder subtypes, to fulminant disease in aggressive sub-types.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that belinostat 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. Such mechanism of action has the potential to translate into clinical efficacy. This is suggested by preclinical studies showing increased antineoplastic activity when belinostat was given in combination with some of the currently used antineoplastic agents for the treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated). In addition the sponsor supported the significant benefit with early clinical data demonstrating tumour response to belinostat.

A positive opinion for belinostat, for treatment of peripheral T-cell lymphoma (nodal, other extranodal and leukaemic/disseminated), was adopted by consensus.

2.2.6 For treatment of hepatic encephalopathy, - EMA/OD/101/12
[Co-ordinators: M. Možina / S. Tsigkos]

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

- Proposed orphan indication

The sponsor is 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 is 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 is also invited to recalculate the prevalence including all the excluded aetiologies and stages of hepatic encephalopathy.

- Significant benefit

The sponsor is invited to elaborate on the significant benefit of the proposed product, taking into account the paucity of data on long-term outcomes, with particular regard to survival. In addition the sponsor is 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 presented clinical studies, and the possible confounding by concomitant causal factors (e.g. benzodiazepine intoxication) in a number of clinical studies among those cited.

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

The COMP adopted a list of issues that will be sent to the sponsor. It was agreed to proceed with nomination of experts for the application assessment. The sponsor will be invited to an oral explanation before the Committee at the October meeting.

2.2.7 For treatment of macular telangiectasia type 2, - EMA/OD/160/11
[Co-ordinators: V. Saano / S. Tsigkos]

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

To the purpose of orphan designation, the sponsor is advised to revise the name of the product.

- 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 is invited to further elaborate on:

- the relevance and applicability of the results obtained with neurotrophic factor 4 in the retina of a Vldlr -/- model to the proposed condition Macular telangiectasia type 2, 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

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 October meeting.

2.2.8 Humanised monoclonal IgG4 antibody against tissue factor pathway inhibitor for treatment of haemophilia A, Novo Nordisk A/S - EMA/OD/095/12
[Co-ordinators: K. Westermark / L. Fregonese]

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

Haemophilia A 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 used valid sources for estimating the

prevalence, including literature searches, national registries, and publications from the World Haemophilia Foundation.

The condition is life-threatening and chronically debilitating due to spontaneous bleeding episodes as well as substantially prolonged bleeding upon injury. Approximately 80-85% of bleeding episodes occur in the muscles and joints of the elbows, knees and ankles, causing acute haemarthrosis and synovitis. Recurrent bleeds in the same location lead to chronic arthropathy, muscular atrophy and deformities. In young children with severe haemophilia, spontaneous bleeds occur within the first 2 years of life, after the child starts to walk. Rare but life-threatening bleeds also occur in the central nervous system, throat, neck, and gastrointestinal tract.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that Humanised monoclonal IgG4 antibody against tissue factor pathway inhibitor may be of significant benefit to those affected by the condition. This appears justified by a clinically relevant advantage based on a new mechanism of action, as the product targets the tissue factor pathway inhibitor, an enzyme involved in the production of factor Xa of the coagulation, resulting in continuous production of factor Xa. This improves the coagulation process bypassing the need of factor VIII, the coagulation factor which is deficient in Haemophilia A. The potential translation of this mechanism of action into clinical efficacy is supported by preclinical results showing prevention of bleeding in animal models. Another advantage of the proposed product is based on a more convenient administration route linked to the possibility of subcutaneous administration. This has also been demonstrated by the sponsor in animal models, where the subcutaneous administration had similar efficacy as the intravenous administration.

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

Due to the lack of quorum the COMP opinion for humanised monoclonal IgG4 antibody against tissue factor pathway inhibitor, for treatment of haemophilia A will be adopted via written procedure.

Post-meeting note:

The draft Summary Report with the grounds for a positive opinion was circulated on 7 September and adopted on 12 September.

2.2.9 For treatment of glioma, - EMA/OD/092/12
[Co-ordinators: D. O'Connor / L. Fregonese]

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

- Proposed indication

The COMP has previously designated glioma as distinct medical entity. The sponsor is 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 is 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 is also invited to better describe the results of the tumour growth.

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

- Prevalence

The sponsor is 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 is 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 is 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.

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 October meeting.

2.2.10 **Lurbinectedin** for treatment of ovarian cancer, Pharma Mar SA Sociedad Unipersonal - EMA/OD/099/12

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

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 approximately 2.8 in 10,000 people in the European Union, at the time the application was made; this was based on data derived from Globocan and Eurocare.

The sponsor has provided satisfactory argumentation to establish that the condition is chronically debilitating, in particular due to abdominal pain or discomfort, an abdominal mass, bloating, back pain, urinary urgency, constipation, tiredness and a range of other non-specific symptoms, as well as more specific symptoms such as pelvic pain, abnormal vaginal bleeding or involuntary weight loss. There can be a build-up of fluid (ascites) in the abdominal cavity. The life threatening nature of the condition is associated with the fact that most patients with ovarian cancer have widespread disease at presentation. This may be partly explained by the relatively early spread of high grade papillary serous cancers to the rest of the peritoneal cavity. Five year survival in Europe has been estimated to be 40%.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that lurbinectedin 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 non-clinical data using an ovarian cancer xenograft model in which when used in monotherapy and potentially better effects to cisplatin.

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

2.2.11 For treatment of thymic epithelial tumours, - EMA/OD/093/12
[Co-ordinators: B. Dembowska-Bagińska / S. Tsigkos]

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

- 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 should 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 is also invited to further elaborate on the particulars and the assessments of the two responders and on any preliminary data from studies. As there are validated models to study the effects of products on this condition the sponsor is invited to elaborate further on the lack of pre-clinical data.

- Prevalence

The sponsor is 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.

Due to the lack of quorum the COMP list of issues will be adopted via written procedure.

Post-meeting note:

The draft Summary Report with the list of issues was circulated on 7 September. The COMP list of issues as adopted by the COMP on 12 September was sent to the sponsor. The sponsor was invited to an oral explanation before the Committee at the October meeting.

2.2.12 Obinutuzumab for treatment of chronic lymphocytic leukemia, Roche Registration Limited - EMA/OD/102/12
[Co-ordinators: B. Dembowska-Bagińska / L. Fregonese]

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

Chronic lymphocytic leukaemia was estimated to be affecting approximately 3 in 10,000 people in the European Union, at the time the application was made. The sponsor used valid epidemiologic sources, mainly international registries, for the prevalence calculation.

The condition is life-threatening and chronically debilitating due to development of bone marrow failure with anaemia, neutropaenia, thrombocytopaenia, and due to lymphadenopathy, splenomegaly, hepatomegaly, and to impaired production of immunoglobulins leading to increased susceptibility to infections. The individual survival time is variable, from less than 2 years in more aggressive disease to 20 years or more in milder forms.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, sufficient justification has been provided that obinutuzumab may be of significant benefit to those affected by the condition. This appears justified in particular with regards to a potential clinically

relevant advantage supported by preclinical and preliminary clinical data. The most important data presented by the sponsor include: preclinical data where obinutuzumab showed higher efficacy than rituximab on tumour growth; and early Phase II clinical data where survival of relapsed chronic lymphocytic leukaemia patients treated with obinutuzumab compared favourably with historical results in relapsed treated with rituximab.

Due to the lack of quorum the COMP opinion for obinutuzumab, for treatment of chronic lymphocytic leukaemia will be adopted via written procedure.

Post-meeting note:

The draft Summary Report with the grounds for a positive opinion was circulated on 7 September and adopted by the COMP on 12 September.

2.2.13 For treatment of small cell lung cancer, - EMA/OD/098/12
[Co-ordinators: D. O'Connor / S. Tsigkos]

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

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

Due to the lack of quorum the COMP list of issues will be adopted via written procedure.

Post-meeting note:

The draft Summary Report with the list of issues was circulated on 7 September. The COMP list of issues as adopted on 12 September was sent to the sponsor.

2.2.14 For treatment of myelodysplastic syndrome, - EMA/OD/051/12
[Co-ordinators: R. Elbers / S. Tsigkos]

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

- Medical plausibility

To establish if a scientific rationale exists for the development of the product for treatment of myelodysplastic syndrome, the sponsor is 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 is asked to provide data from relevant models to support the plausibility of this products 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 is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the in vitro studies to justify the assumption of significant benefit over authorised medicinal products e.g. erythropoietin for the proposed orphan indication.

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

2.2.15 Recombinant human lecithin cholesterol acyltransferase for treatment of lecithin cholesterol acyltransferase deficiency, Alphacore Pharma Limited - EMA/OD/091/12
[Co-ordinators: H. Bosch-Traberg / S. Tsigkos]

The Committee agreed that the condition, lecithin cholesterol acyltransferase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

Lecithin cholesterol acyltransferase deficiency was estimated to be affecting approximately 0.001 in 10,000 people in the European Union, at the time the application was made.

The condition is chronically debilitating due to corneal opacities that impair vision and the development of normochromic haemolytic anaemia, and life threatening due to renal impairment that may lead to end-stage renal disease.

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

Due to the lack of quorum the COMP opinion for recombinant human lecithin cholesterol acyltransferase, for treatment of lecithin cholesterol acyltransferase deficiency will be adopted via written procedure.

Post-meeting note:

The draft Summary Report with the grounds for a positive opinion was circulated on 7 September and adopted by the COMP on 12 September.

2.2.16 Liposomal daunorubicin for treatment of acute myeloid leukaemia, Galen Limited - EMA/OD/105/12 (active time: day 27)
[Co-ordinators: R. Elbers / S. Tsigkos]

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

Acute myeloid leukaemia was estimated to be affecting not more than 1.2 in 10,000 people in the European Union, at the time the application was made.

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, sufficient justification has been provided that liposomal daunorubicin may be of significant benefit to those affected by the condition. This appears justified in particular with regards to the pharmacokinetic properties of the liposomal formulation. This can translate into a clinically relevant advantage due to a more selective distribution of the antineoplastic agent to the neoplastic tissue. This has the potential of achieving a better cardiac safety profile than non-liposomal daunorubicn and increasing the antineoplastic activity. The potential clinical relevant advantage is supported by early clinical data in a paediatric population of relapsed patients, where the product significantly increased the remission rate when added to currently authorised regimens for the treatment of acute myeloid leukaemia.

A positive opinion for liposomal daunorubicin for treatment of acute myeloid leukaemia, was adopted by consensus.

2.3. COMP opinions adopted via written procedure following July meeting

2.3.1 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

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 folate receptor positive ovarian cancer, Endocyte Europe B.V. - EMA/OD/056/12
[Co-ordinators: B. Dembowska-Bagińska / L. Fregonese]

The final Summary report with grounds for positive opinion as adopted via written procedure on 23 July (EMA/COMP/399658/2012) was circulated for information in the pre-mailing.

2.3.2 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

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 folate receptor positive ovarian cancer, Endocyte Europe B.V. - EMA/OD/055/12
[Co-ordinators: B. Dembowska-Bagińska / L. Fregonese]

The final Summary report with grounds for positive opinion as adopted via written procedure on 23 July (EMA/COMP/399309/2012) was circulated for information in the pre-mailing.

2.4. Evaluation on-going

The Committee noted that evaluation was on-going for 29 applications for orphan designation.

2.5. Validation on-going

The Committee was informed that validation was on-going for 24 applications for orphan designation.

3. Requests for protocol assistance

3.1 For treatment of amyotrophic lateral sclerosis [Coordinator: B. Bloechl-Daum]

The protocol assistance letter was adopted by the Committee.

3.2 For prevention of oral mucositis in head and neck cancer patients undergoing radiation therapy [Coordinator: B. Bloechl-Daum]

The draft COMP response to the sponsor's question on significant benefit was tabled and adopted.

3.3 For treatment of primary myelofibrosis [Coordinator: R. Elbers]

The protocol assistance letter was adopted by the Committee.

Post-meeting note:

The protocol assistance letter for treatment of leishmaniasis; [Coordinator: B. Bloechl-Daum)] was circulated on 7 September for adoption via written procedure and was adopted by the COMP on 12 September.

4. Overview of applications

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

COMP co-ordinators were appointed for 8 applications submitted and 32 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 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 was informed that the CHMP adopted a positive opinion during their July 2012 meeting.

The COMP concluded that:

- Treatment of anaplastic large cell lymphoma (OD/072/08, EU/3/08/595)

The sponsor has been granted two orphan designations for monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin as a medicinal product; firstly for the "treatment of Hodgkin lymphoma" (EU/3/08/596) and secondly for the "treatment of anaplastic large cell lymphoma" (EU/3/08/595).

The proposed therapeutic indication "treatment of patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): 1) following autologous stem cell transplant or 2) following at least two prior therapies when autologous stem cell transplantation is not a treatment option and treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL)." falls entirely within the scope of the abovementioned orphan indications of the designated Orphan Medicinal Product.

The prevalence of anaplastic large cell lymphoma was estimated to be 0.2 in 10,000 and remains below 5 in 10,000 at the time of the review of the designation criteria.

The condition is life-threatening with a 5-year survival of 29-44%.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin may be of potential significant benefit to those affected by the orphan condition still holds. Patients with refractory and relapsed anaplastic large cell lymphoma who no longer responded to any therapy showed prolonged survival time when treated with monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin.

An opinion not recommending the removal from the EC Register of Orphan Medicinal Products was adopted by consensus.

- Treatment of Hodgkin lymphoma (OD/073/08, EU/3/08/596)

The sponsor has been granted two orphan designations for monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin as a medicinal product; firstly for the "treatment of Hodgkin lymphoma" (EU/3/08/596) and secondly for the "treatment of anaplastic large cell lymphoma" (EU/3/08/595).

The proposed therapeutic indication "treatment of patients with relapsed or refractory CD30+ Hodgkin lymphoma (HL): 1) following autologous stem cell transplant or 2) following at least two prior therapies when autologous stem cell transplantation is not a treatment option and treatment of patients with relapsed or refractory systemic anaplastic large cell lymphoma (sALCL)." falls entirely within the scope of the abovementioned orphan indications of the designated Orphan Medicinal Product.

The prevalence of Hodgkin lymphoma was estimated to be 1 in 10,000 and remains below 5 in 10,000 at the time of the review of the designation criteria.

The condition is chronically debilitating and life threatening due to the poor long-term prognosis in patients that progress during or shortly after initial chemotherapy.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin may be of potential significant benefit to those affected by the orphan condition still holds. Patients with relapsed or refractory CD30+ Hodgkin lymphoma who no longer responded to any therapy showed prolonged survival time when treated with monoclonal antibody against human CD30 covalently linked to the cytotoxin monomethylauristatin.

An opinion not recommending the removal from the EC Register of Orphan Medicinal Products was adopted by consensus.

5.1.2 Glybera (Adeno-associated viral vector expressing lipoprotein lipase) for treatment of lipoprotein lipase deficiency; Amsterdam Molecular Therapeutics BV., (OD/079/03, EU/3/04/194) [Co-ordinators: V. Stoyanova / S. Mariz]

The COMP concluded that:

The proposed therapeutic indication (*Glybera, indicated for adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. The diagnosis of LPLD has to be confirmed by genetic testing. The indication is restricted to patients with detectable levels of LPL protein)* falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product (treatment of lipoprotein lipase deficiency).

The prevalence of lipoprotein lipase deficiency was estimated to be 0.02 in 10,000 and remains below 5 in 10,000 at the time of the review of the designation criteria.

The condition is life-threatening and chronically debilitating due to patients presenting with chylomicronemia and very severe hypertriglyceridemia (SHTG), as a result of absent or markedly decreased LPL activity. Symptoms and signs of the condition may be present as of infancy, although less severely progressing disease may lead to clinically detected events only later in life. Complications include recurrent acute pancreatitis which leads to progressive risk of diabetes mellitus. There may be an increased risk of premature coronary artery disease as well. The most severe complication associated with LPL deficiency is acute haemorrhagic pancreatitis which itself is life-threatening.

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

An opinion not recommending the removal from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft Public Summary of the COMP opinion (EMA/571233/2012) was adopted for publication on the EMA website.

5.1.3 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: B. Sepodes / L. Fregonese].

The COMP noted the CHMP negative opinion as adopted in July 2012.

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:

- for the treatment of infrequently transfused beta-thalassemia major patients
- for 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].

5.2.5 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].

5.3. On-going procedures

5.3.1 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: TBC / TBC].

5.3.2 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].

5.3.3 Delamanid ((R)-2-Methyl-6-nitro-2-{4-[4-(4-trifluoromethoxyphenoxy)piperidin-1-yl]phenoxymethyl}-2,3-dihydroimidazo[2,1-b]oxazole) for treatment of tuberculosis (OD/094/07, EU/3/07/524); Otsuka Novel Products GmbH [Co-ordinators: V. Stoyanova / L. Fregonese].

5.3.4 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].

5.3.5 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].

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

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

5.3.8 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].

5.3.9 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].

5.3.10 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].

5.3.11 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].

5.3.12 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. Thorsteinson / TBC].

5.4. COMP opinion adopted via written procedure following July meeting

5.4.1 Dacogen (Decitabine) for treatment of acute myeloid leukaemia; Janssen-Cilag International NV (OD/004/06, EU/3/06/370) [Co-ordinators: R. Elbers / S. Tsigkos]
CHMP opinion adopted in July 2012.

The final report on review of OMP designation with grounds for positive opinion EMA/COMP/442447/2012 as adopted on 2 August was circulated for information. The draft Public Summary of the COMP opinion EMA/COMP/558969/2012 was adopted.

6. Procedural aspects

6.1 Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver)

The EMA Policy EMA/272931/2011 was circulated in the pre-mailing. The presentation was postponed.

6.2 Orphan products under the PDCO evaluation with start of procedure 11 June 2012

The Committee noted the on-going procedures.

7. Any other business

7.1 Informal COMP meeting

The draft Minutes of COMP/CAT/PCDO meeting held on 24 May 2012 in Copenhagen were adopted and the draft Agenda for the COMP/PDCO informal meeting to be held on 22 November 2012 in Rome was circulated for information.

7.2 EMA - FDA and EU - Japan collaboration

The draft Agenda for the EMA/FDA teleconference to be held on 10 September 2012 and the draft Agenda for the FDA/EMA Orphan Designation and Grant Workshop to be held on 7-13 October 2012 in Washington D.C. were circulated in the pre-mailing for information.

Date of next COMP meeting: 3 - 5 October 2012

Annex A

List of participants on 4 - 5 September 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
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
Dainis Krievins	Latvija
Aušra Matulevičienė	Lietuva
Judit Eggenhofer	Magyarország
Albert Vincenti	Malta
Violeta Stoyanova	Nederland
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Österreich
Bożenna Dembowska-Bagińska	Polska
Ana Corrêa-Nunes	Portugal
Flavia Saleh	Romãnia
Martin Možina	Slovenija
Veijo Saano	Suomi/Finland
Kerstin Westermark	Sverige
Daniel O'Connor	United Kingdom
Pauline Evers	Patient representative representing the European Genetic Alliances Network
Birthe Byskov Holm	Volunteer patient representative for Eurordis
János Borvendég	CHMP Representative
Aikaterini Moraiti	CHMP Representative
Vacant	EMA Representative

Observers:

Ivana Martinovic	Croatia
Maria Mavris	Eurordis

European Commission:

Mirjam Soderholm	DG Health and Consumers

EMA Secretariat:

Jordi Llinares Garcia	Head of Orphan Medicines Section

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

Apologies:

Heidrun Bosch-Traberg	Danmark
Ioannis Kkolos	Κύπρος
Henri Metz	Luxembourg
Milica Molitorisová	Slovensko