EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 August 2014
EMA/COMP/220006/2014
Procedure Management and Business Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes of the 13-14 May 2014 meeting

Note on access to documents

Some documents mentioned in the agenda/minutes cannot be released at present within the framework of Regulation (EC) No 1049/2001 on access to documents because they are subject to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

Contents

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. Introduction

1.1 Adoption of the agenda, EMA/COMP/219134/2014

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 8-10 April 2014 EMA/COMP/151064/2014

The adoption was postponed.

1.3 Conflicts of Interest

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

K. Kubáčková declared a potential conflict of interest on agenda point 2.2.9 and 5.1.1.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Product for treatment of non-infectious uveitis - EMA/OD/014/14
[Co-ordinators: K. Westermark]

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:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of non-infectious uveitis, the sponsor should further elaborate on the validity of the use of preclinical and clinical data obtained with suprachoroidal injectable suspension with a different product authorised for a different indication, to support the medical plausibility of their product.

- Number of people affected

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

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the advantages of their product compared with other authorised treatments.

In the written response, and during an oral explanation before the Committee on 13 May 2014, the sponsor elaborated on the similarities and differences of the product used for the purpose of establishing the medical plausibility and the product as applied for designation. With regards to the prevalence, the sponsor reviewed country-specific data for different Member States and commented on their validity. Finally, with regards to the significant benefit, the sponsor argued significant benefit on

[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).

the basis of an alternative mode of administration, directly accessing the pathologies of the disease in the choroid and outer retina. This was argued to have the potential to lead to improved outcomes and safety profile.

The Committee considered that in the absence of data with the specific product as applied for designation in relevant settings of the condition, it would be difficult to consider the intention to treat and significant benefit issues satisfactorily resolved and a negative trend was noted.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 May 2014, prior to final opinion.

2.1.2 Product for treatment of amyotrophic lateral sclerosis - EMA/OD/007/14

[Co-ordinators: V. Stoyanova]

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:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of amyotrophic lateral sclerosis, the sponsor should provide further details on:

  - the methodology in the SOD1 mice studies, including inflammatory and functional endpoints, and how symptom progression was measured;
  - the results obtained in the SOD1 mice studies, and the relevance to the proposed use of the product.

The sponsor is also invited to clarify which, among the ones presented in this section, are sponsor's generated data, and indicate the appropriate references for non-sponsor's generated data.

- Number of people affected

The sponsor is invited to further elaborate on the methods used to reach the proposed prevalence figure, which is lower than what previously designated by the Committee.

- Significant benefit

In order to support the significant benefit the sponsor is requested to further discuss the protocol and the data of the non-sponsor generated Phase II clinical study and presented in this application and in particular:

  - the baseline characteristics of the participants in the study;
  - the choice of endpoints, with clarification on whether any other clinical endpoints have been studied;
  - the way the pre-treatment values for the ALSFRS-R score have been generated, and their values for comparison;
  - the relevance of the changes reported in the ALSFRS-R score at 6 months on top of riluzole in supporting the clinically relevant advantage of adding the proposed product to riluzole.

Furthermore, it would be useful to have clarification about the sponsor' participation in the above study and to obtain more information on the on-going study and planned development programme of the

sponsor with the proposed product.

In the written response, and during an oral explanation before the Committee on 13 May 2014, the sponsor elaborated on the available data in the public domain pertaining to another product containing the same active substance, and also further elaborated on the prevalence issue as requested by the Committee. The Committee considered that in the absence of data with the new proposed formulation as applied for designation and the limited data available for the non-sponsor generated studies, it would be difficult to consider the justification of medical plausibility and significant benefit satisfactorily resolved.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 14 May 2014, prior to final opinion.

2.1.3 **Isavuconazonium sulfate** for treatment of invasive aspergillosis, Basilea Medical Ltd. - EMA/OD/009/14 *[Co-ordinators: A. Moraiti]*

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:

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit and in particular:

- the relevance of the efficacy results of the study showing non-inferiority between isavuconazole and voriconazole, taking into account the high rate of discontinuation for insufficient therapeutic response in the group treated with isavuconazole;
- the claimed significant benefit on the grounds of an improved safety profile, and in particular:

The different dosing regimens used in the phase III study as compared to the phase II study, and the implications for safety.

The occurrence of fewer adverse events with isavuconazole in only three organ classes and the relevance of this to clinical safety.

In the written response, and during an oral explanation before the Committee on 13 May 2014, the sponsor further elaborated on the issues raised.

Regarding the rate of discontinuation in the non-inferiority study the sponsor reported that study discontinuation rates were similar for both isavuconazole and voriconazole respectively. The sponsor explained that determining treatment discontinuation was left to the discretion of the investigator, and practices in defining the primary reason for discontinuation of treatments, especially in cases when patients had more than one reason for discontinuation might have been different in different centres. It was also discussed that the results of the study on the primary endpoint of all-cause mortality and the secondary endpoint of overall response at end of treatment indicated a comparable efficacy, therefore supporting the therapeutic non-inferiority of the product.

Regarding the main claim for significant benefit, the sponsor presented data on all organ classes and claimed a lower rate of adverse events particularly in eye disorders, skin and subcutaneous tissue and hepatobiliary disorders. The Committee agreed that the condition, invasive aspergillosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing isavuconazonium sulfate was considered justified based on preclinical data showing improved survival with the proposed product.

The condition is life-threatening due to progressive dyspnoea, pleuritic chest pain, haemoptysis, and due to dissemination of the infection to several organs including the brain. Mortality rates are up to 70–95% in recipients of bone marrow transplant.

The condition was estimated to be affecting less than 2 in 10,000 persons 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 isavuconazonium sulfate may be of significant benefit to those affected by the condition. The sponsor has provided clinical data showing an improved safety profile, in particular in terms of hepatic safety, as compared to the currently authorized products for the treatment of this condition. The Committee considered that this constitutes a clinically relevant advantage for the patient population affected by invasive aspergillosis.

The COMP therefore recommends the designation of this medicinal product, containing isavuconazonium sulfate, as an orphan medicinal product for the orphan indication: treatment of invasive aspergillosis.

A positive opinion for Isavuconazonium sulfate, for treatment of invasive aspergillosis, was adopted by consensus.

2.1.4 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1Hindol-5-yl}cyclopropanecarboxamide for treatment of cystic fibrosis, Vertex Pharmaceuticals (U.K.) Limited - EMA/OD/002/14
[Co-ordinators: J. Eggenhofer]

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:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of cystic fibrosis, the sponsor should further elaborate on:

  - the results obtained on the expression of the corrected CFTR in vitro, and in particular the choice of the cut-off restoration of function to 10% of WT CFTR, and the clinical relevance of such restoration;
  - the clinical relevance of the results on chloride transport with the level of correction induced by the product.

- Significant benefit

The sponsor is requested to further discuss the data provided for supporting significant benefit and in particular the results of the arm(s) where the proposed product was used in monotherapy in clinical phase.

In the written response, and during an oral explanation before the Committee on 13 May 2014, the sponsor discussed that epidemiological studies suggest that severe CF disease in patients with F508del mutation is associated with a CFTR function of less than 10%. Chloride transport levels used to

establish the severity of the disease and their correlation with in vivo studies of mutant CFTR function were discussed within the context of establishing WT CFTR function as a minimum criteria for clinical candidate selection. With regards to the significant benefit, the sponsor further discussed the results from a Phase 2, multicenter, randomized, double blind trial of the proposed product as a monotherapy, and in combination with ivacaftor in subjects who are homozygous or heterozygous for the F508del-CFTR mutation.The Committee agreed that the condition, cystic fibrosis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropanecarboxamide was considered justified based on preclinical data showing partial correction of the chloride transport defect in cells from cystic fibrosis patients.

The condition is chronically debilitating and life threatening due to the recurrent and resistant respiratory infections with development of bronchiectasis and terminal respiratory failure.

The condition was estimated to be affecting approximately 0.8 in 10,000 persons 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-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropanecarboxamide may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical results showing improvement of lung function when the proposed product, increasing expression of the CFTR protein, is used in combination with a product that increases the function of the CFTR protein. The Committee considered that the mechanism of action of the product directly targeting the mutated channel protein in cystic fibrosis has the potential to translate into a clinically relevant advantage for the patients affected by cystic fibrosis through higher clinical efficacy and the possible use of the product in combination with some of the currently authorized treatments for cystic fibrosis.

A positive opinion for 1-(2,2-difluoro-1,3-benzodioxol-5-yl)-N-{1-[(2R)-2,3-dihydroxypropyl]-6-fluoro-2-(1-hydroxy-2-methylpropan-2-yl)-1H-indol-5-yl}cyclopropanecarboxamide, for treatment of cystic fibrosis, was adopted by consensus.

2.1.5 Mixture of two adeno-associated viral vectors of serotye 8 containing the 5'-half sequence of human *ABCA4* gene and the 3'- half sequence of human *ABCA4* gene for treatment of Stargardt's disease, Fondazione Telethon - EMA/OD/005/14

[Co-ordinators: J. Torrent-Farnell]

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:

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Stargardt's disease, the sponsor should further:

  - elaborate on the specific particulars of the dual vectors proposed for designation, specifying the promoter of the mixture as applied for designation;

- elaborate on the relevance of the data submitted for the specific product as applied for designation, since it appears that several different mixtures with different promoters and serotypes are used for the justification of the intention to treat;
- specify which data pertain to the specific mixture proposed for designation, with relevance to the above questions.

In the written responses, the sponsor further clarified the serotype of the vectors and the promoter used in the proposed product, and specified in detail which vectors were used in the corresponding studies as reported in the application. The COMP, after reviewing the responses considered that an oral explanation was not necessary. 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 condition with the medicinal product containing mixture of two adeno-associated viral vectors of serotype 8 containing the 5'-half sequence of human ABCA4 gene and the 3'-half sequence of human ABCA4 gene was considered justified based on pre-clinical in vivo data which showed improved recovery from light desensitization.

The condition is chronically debilitating, in particular due to loss of visual acuity and central vision loss, which may progress to complete blindness.

The condition was estimated to be affecting approximately 1.5 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for Mixture of two adeno-associated viral vectors of serotye 8 containing the 5'-half sequence of human *ABCA4* gene and the 3'-half sequence of human *ABCA4* gene, for treatment of Stargardt's disease, was adopted by consensus.

2.1.6 Mixture of two adeno-associated viral vectors serotype 8 containing the 5'-half sequence of human *MYO7A* gene and the 3'- half sequence of human *MYO7A* gene for treatment of Usher syndrome, Fondazione Telethon - EMA/OD/004/14

[Co-ordinators: A. Magrelli]

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:

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of Usher syndrome, the sponsor should further:

- elaborate on the specific particulars of the dual vectors proposed for designation, specifying the promoter of the mixture as applied for designation;
- elaborate on the relevance of the data submitted for the specific product as applied for designation, since it appears that several different mixtures with different promoters and serotypes are used for the justification of the intention to treat;
- specify which data pertain to the specific mixture proposed for designation, with relevance to the above questions.

In the written responses, and as discussed in the plenary meeting by the Committee on 14 May 2014, the sponsor further clarified the serotype of the vectors and the promoter used in the proposed product, and specified in detailed which vectors were used in the corresponding studies as presented in the application. The COMP after reviewing the responses considered that an oral explanation was not necessary.

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

The intention to treat the condition with the medicinal product containing mixture of two adeno-associated viral vectors of serotype 8 containing the 5'-half sequence of human MYO7A gene and the 3'-half sequence of human MYO7A gene was considered justified based on preclinical data showing expression of the missing protein and improvements in histological outcomes in a relevant model of the condition.

The condition is chronically debilitating due to the development of nyctalopia and loss of visual fields, sensorineural hearing loss and vestibular dysfunction leading to balance defects.

The condition was estimated to be affecting less than 1 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for Mixture of two adeno-associated viral vectors serotype 8 containing the 5'-half sequence of human *MYO7A* gene and the 3'-half sequence of human *MYO7A* gene, for treatment of Usher syndrome, was adopted by consensus.

2.1.7 Product for treatment of chronic lymphocytic leukaemia/ small lymphocytic lymphoma - EMA/OD/195/13
[Co-ordinators: K. Kubáčková]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 24 April 2014, prior to responding to the list of issues.

2.1.8 Product for treatment of Glucose Transporter Type-1 Deficiency Syndrome - EMA/OD/011/14
[Co-ordinators: A. Corrêa Nunes]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 24 April 2014, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1 Adeno-associated viral vector serotype 2 containing the human *REP1* gene for treatment of choroideremia, NightstaRx Ltd. - EMA/OD/033/14

[Co-ordinators: V. Stoyanova]

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

The intention to treat the condition with the medicinal product containing adeno-associated viral vector serotype 2 containing the human *REP1* gene was considered justified based on preliminary clinical data showing improvement of visual acuity with the proposed treatment.

The condition is chronically debilitating due to nyctalopia, loss of visual fields, tunnel vision, and eventually vision loss;The condition was estimated to be affecting not more than 0.3 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for Adeno-associated viral vector serotype 2 containing the human *REP1* gene, for treatment of choroideraemia, was adopted by consensus.

2.2.2 Afamelanotide for treatment of familial benign chronic pemphigus (Hailey-Hailey disease), Clinuvel UK Limited - EMA/OD/019/14
[Co-ordinators: A. Lorence]

The Committee agreed that the condition, familial benign chronic pemphigus (Hailey-Hailey disease), is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing afamelanotide was considered justified based on preclinical and preliminary clinical data.

The condition is chronically debilitating due to recurrent painful blisters that may become infected and affect the quality of the life of the patients.

The condition was estimated to be affecting not more than 0.2 in 10,000 persons in the European Union, at the time the application was made.

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

A positive opinion for Afamelanotide, for treatment of familial benign chronic pemphigus (Hailey-Hailey disease), was adopted by consensus.

2.2.3 Beloranib for treatment of Prader-Willi syndrome, Dr Ulrich Granzer - EMA/OD/023/14
[Co-ordinators: V. Tillmann]

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

The intention to treat the condition with the medicinal product containing beloranib was considered justified based on pre-clinical in vivo and preliminary clinical data in patients with the condition who showed an improvement in parameters associated with weight loss.

The condition is life-threatening and chronically debilitating, in particular due to cognitive impairment, maladaptive behaviour and morbid obesity.

The condition was estimated to be affecting approximately 0.33 in 10,000 persons 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 beloranib may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical and preliminary clinical data that demonstrate that the product reduces the hyperphagia associated with the condition thereby inducing weight loss by a mechanism which is different from other anti-obesity therapies. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Beloranib, for treatment of Prader-Willi syndrome, was adopted by consensus.

2.2.4 Product for treatment of systemic amyloidosis - EMA/OD/020/14

[Co-ordinators: K. Westermark]

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

- Proposed condition

As per the 2012 recommendations from the Nomenclature committee of the International Society of Amyloidosis (Sipe *et al* Amyloid 19(4) 167-70) and in line with the opinion of the Committee, the sponsor is requested to apply for the treatment of distinct medical entities.

For the purposes of orphan medicinal product designation attention is drawn to the Orphan regulations and guidelines (especially section A of ENTR/6283/00 Rev04).

- Intention to diagnose, prevent or treat

To establish correctly the medical plausibility, the sponsor should further elaborate on the following issues:

  - the argued obligate partnership between the two products applied for designation, by providing data that shows that neither of these products may have effects alone;
  - any specific data obtained with the product(s) from the on-going studies either in models or in patients affected by the condition;
  - the methodology used in the pre-clinical studies as well as the results from these studies and their relevance for the development of the product in the condition.

- Life-threatening and debilitating nature of the condition

For the amended indication (s), the sponsor should further elaborate on the life-threatening or chronically debilitating nature of the condition.

- Number of people affected

For the amended indication (s), the sponsor should also recalculate the prevalence. For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

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

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential for improved efficacy in the condition. The sponsor is requested to further discuss the arguments provided for significant benefit based on data, and provide a comparative discussion versus authorised counterparts.

The sponsor should also detail the results of any clinical studies 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 for a written response and during an oral explanation before the Committee at the June meeting.

2.2.5 Product for treatment of cystinosis - EMA/OD/031/14

[Co-ordinators: A. Magrelli]

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

- Intention to diagnose, prevent or treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of cystinosis, the sponsor should further elaborate on:

  - the results obtained in vitro on cell lines;
  - the relevance of the preclinical model used for the treatment of cystinosis, and the interpretation of the results obtained in the experiments;
  - the methodology used in the pre-clinical studies as well as the results from these studies and their relevance for the development of the product in the condition.

Number of people affected

The submitted prevalence calculation appears to be quite high. The sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition and resubmit to the COMP.

- Significant benefit

The arguments on significant benefit are based a major contribution to patient care.

The sponsor is requested to further discuss the arguments provided for significant benefit and to clarify how the results from the in vitro fibroblast cell study could justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor should discuss the place of non-clinical in vivo models which could confirm the in vitro data presented.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the June meeting.

2.2.6 **Humanised Fc Engineered Monoclonal Antibody against CD19** for treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma, MorphoSys AG - EMA/OD/022/14

[Co-ordinators: K. Kubáčková]

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

The intention to treat the condition with the medicinal product containing humanised Fc engineered monoclonal antibody against CD19 was considered justified based on preclinical data showing reduction of tumour growth, and preliminary data showing favourable clinical responses.

The condition is chronically debilitating and life-threatening due to development of anaemia, neutropenia, thrombocytopenia, lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulins leading to increased susceptibility to infections.

The condition was estimated to be affecting approximately 3 in 10,000 persons 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 humanised Fc engineered monoclonal antibody against CD19 may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate favourable responses with the product in patients relapsing after previous treatments. Additionally, preclinical data show enhanced reduction of tumour growth in combination with some of the currently authorised products, suggesting the possibility of an improved efficacy when the product is used in combination in clinical setting. The Committee considered that the above constitutes a clinically relevant advantage for the patients affected by chronic lymphocytic leukaemia / small lymphocytic lymphoma.

A positive opinion for Humanised Fc engineered monoclonal antibody against CD19, for treatment of chronic lymphocytic leukaemia /small lymphocytic lymphoma, was adopted by consensus.

2.2.7 Product for treatment of plasma cell myeloma - EMA/OD/035/14

[Co-ordinators: B. Dembowska-Bagińska]

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

- Prevalence

The sponsor is invited to further justify the duration of the condition used for the calculation of prevalence and if necessary recalculate the estimate taking into account the most recent information on the prognosis of these patients.

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit in particular with regards to the authorised proteasome inhibitor.

The sponsor is also invited to elaborate on the background treatments of the relapsed/refractory patients who participated in the preliminary clinical studies presented as part of the application.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the June meeting.

2.2.8 **Norursodeoxycholic acid** for treatment of primary sclerosing cholangitis, Dr Falk Pharma GmbH - EMA/OD/026/14

[Co-ordinators: L. Gramstad]

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

The intention to treat the condition with the medicinal product containing norursodeoxycholic acid was considered justified based on preclinical data showing improved liver biochemistry, histology, and bile flow.

The condition is chronically debilitating and life-threatening due to progressive hepatic dysfunction, with development of portal hypertension and hepatic failure. The patients also have an increased risk of hepatobiliary cancer, including cholangiocarcinoma and gallbladder cancer.

The condition was estimated to be affecting less than 1.6 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 norursodeoxycholic acid may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate improved effects compared to the authorised product with regards to liver function. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Norursodeoxycholic acid, for treatment of primary sclerosing cholangitis, was adopted by consensus.

2.2.9 Product for treatment of diffuse large B-cell lymphoma - EMA/OD/029/14
[Co-ordinators: B. Dembowska-Bagińska]

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

- Significant benefit

In order to justify the significant benefit the sponsor should elaborate more in depth on all available data supporting the assumption of improved efficacy over rituximab in the treatment of DLBCL.

In particular the sponsor is invited to further discuss the potential higher clinical efficacy proposed as a ground for significant benefit as well as a potential advantage of the proposed product when used in combination with currently existing products, including in patients refractory to or relapsing with rituximab.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the June meeting.

2.2.10 Recombinant Human Alpha-1-Microglobulin for treatment of Preeclampsia, A1M Pharma AB - EMA/OD/027/14
[Co-ordinators: B. Bloechl-Daum]

The Committee agreed that the condition, pre-eclampsia 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 alpha-1-microglobulin was considered justified based on non-clinical in vivo studies showing an improvement in blood pressure, a reduction in foetal haemoglobin leakage and an improvement in placental functioning.

The condition is life-threatening due to seizures and risk of maternal death.

The condition was estimated to be affecting approximately 3.8 in 10,000 persons 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 alpha-1-microglobulin may be of significant benefit to those affected by the condition. The sponsor has provided non-clinical in vivo data that demonstrate that the alternative mode of action reduces blood pressure improves placental functioning and reduces foetal haemoglobin leakage which is associated with the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Recombinant human alpha-1-microglobulin, for treatment of pre-eclampsia, was adopted by consensus.

2.2.11 Product for treatment of systemic amyloidosis EMA/OD/021/14
[Co-ordinators: K. Westermark]

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

- Proposed condition

As per the 2012 recommendations from the Nomenclature committee of the International Society of Amyloidosis (Sipe *et al* Amyloid 19(4) 167-70) and in line with the opinion of the Committee, the sponsor is requested to apply for the treatment of distinct medical entities.

For the purposes of orphan medicinal product designation attention is drawn to the Orphan regulations and guidelines (especially section A of ENTR/6283/00 Rev04).

- Intention to diagnose, prevent or treat

To establish correctly the medical plausibility, the sponsor should further elaborate on the following issues:

  - the argued obligate partnership between the two products applied for designation, by providing data that shows that neither of these products may have effects alone;
  - any specific data obtained with the product(s) from the on-going studies either in models or in patients affected by the condition;
  - the methodology used in the pre-clinical studies as well as the results from these studies and their relevance for the development of the product in the condition.

- Life-threatening and debilitating nature of the condition

For the amended indication(s), the sponsor should further elaborate on the life-threatening or chronically debilitating nature of the condition.

- Number of people affected

For the amended indication(s), the sponsor should also recalculate the prevalence. For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

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

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential for improved efficacy in the condition. The sponsor is requested to further discuss the arguments provided for significant benefit based on data, and provide a comparative discussion versus authorised counterparts.

The sponsor should also detail the results of any clinical studies 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 for a written response and during an oral explanation before the Committee at the June meeting.

2.2.12 Product for treatment for necrotizing soft tissue infections - EMA/OD/028/14
[Co-ordinators: S. Thorsteinsson]

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

- Proposed condition

"Necrotizing soft tissue infections" should be justified as a distinct medical entity or a valid subset. Note that this is for the purposes of orphan medicinal product designation attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00 Rev4).

The sponsor should provide any internationally accepted classification or consensus agreement justifying that the condition as proposed for designation is a distinct medical entity, or amend the proposed indication accordingly.

- Intention to diagnose, prevent or treat

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 preclinical models used for the treatment of necrotizing soft tissue infections (or in case of an amended indication, the new indication), and the interpretation of the results obtained in the experiments;
  - the basis for restricting the proposed indication to Necrotizing soft tissue infections, and the relevance of the product for other infections and septic syndromes, notwithstanding that the orphan condition should be a distinct medical entity or a valid subset;
  - the methodology used in the preliminary-clinical study as well as the results from this study and their relevance for the development of the product in the condition;
  - the discrepancy in the level of effects observed in the preclinical and preliminary clinical settings.

Life-threatening and debilitating nature of the condition

In case of amended indication, the seriousness of the condition should be readdressed.

- Number of people affected

In case of amended indication, the prevalence of the condition should be readdressed.

For the calculation and presentation of the prevalence estimate it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation".

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potentially improved efficacy in the condition. The sponsor should detail the results of any clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the June meeting.

2.2.13 Product for treatment of Growth Hormone Deficiency in Adults and Children - EMA/OD/030/14 *[Co-ordinators: V. Tillmann]*

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

- Number of people affected

The sponsor is proposing a range for the prevalence for the condition. Previous designations have given a point estimate.

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

- Significant benefit

The sponsor should further elaborate on the differences between their product and the authorised modified release somatropin. The arguments on significant benefit are based on a modified release formulation offering a clinically relevant advantage based on different pharmacokinetic and pharmacodynamic properties.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the Phase II study to justify the assumption of significant benefit over other modified release authorised medicinal products for the proposed orphan indication.

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

The sponsor should further elaborate on the potential risks with the product and how this compares with the safety profile with regards to immunogenicity of current authorised medicinal products for the same condition.

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the June meeting.

2.2.14 Product for treatment of thrombocytopenia caused by chronic idiopathic thrombocytopenia purpura - EMA/OD/025/14
[Co-ordinators: M. Možina]

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

- Orphan indication

The sponsor is invited to revise the orphan indication taking into account:

  - the plausibility and justifications for restricting the indication to the sub-set of chronic forms of the disease. In this respect the attention of the sponsor is drawn to the Orphan regulations and guidelines clarifying sub-setting of medical conditions (section A of ENTR/6283/00);
  - the current classification of the proposed condition.

- Significant benefit

The sponsor is requested to further elaborate on the results from the PROSORBA study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication

The COMP adopted a list of issues for a written response and during an oral explanation before the Committee at the June meeting.

2.3. Revision on the COMP opinion

2.3.1 Autologous CD34+ cells transduced with a lentiviral vector containing the human *SGSH* gene for treatment of mucopolysaccharidosis IIIA (Sanfilippo A syndrome), Cochamo Systems Ltd - EMA/OD/006/14
[Co-ordinator: J. Torrent-Farnell]

Revised Summary Report was adopted.

2.4. Evaluation on-going

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

2.5. Validation on-going

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

3. Requests for protocol assistance

3.1 For treatment of primary myelofibrosis [Coordinator: A. Magrelli]

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

3.2 For treatment of acute lymphoblastic leukaemia [Coordinator: B. Bloechl-Daum]

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 33 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 Nexavar (Sorafenib tosylate) Bayer HealthCare AG, (extension of indication to include treatment of differentiated thyroid carcinoma):

a) treatment of follicular thyroid cancer (EU/3/13/1199)

b) treatment of papillary thyroid cancer (EU/3/13/1200)

The COMP noted the CHMP opinion on MA adopted at 22-25 April 2014 meeting.

The COMP concluded that:

The approved therapeutic indication “treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine” was considered to fall under the two existing designations “Treatment of follicular thyroid carcinoma” and “Treatment of papillary thyroid carcinoma”. During its meeting of 13 to 14 May 2014, the COMP reviewed the designations EU/3/13/1199 and EU/3/13/1200 for Nexavar (sorafenib) as an orphan medicinal product for the treatment of follicular and papillary thyroid cancers. The COMP assessed whether, at the time of addition of a new indication to the marketing authorisation, the medicinal product still met the criteria for orphan designation. The Committee looked at the seriousness and prevalence of the conditions, and the existence of other methods of treatment. As other methods of treatment are authorised in the European Union (EU), the COMP also considered

whether the medicine is of significant benefit to patients with follicular and papillary thyroid cancer. The COMP recommended that the orphan designations of the medicine be maintained[2].

- Life-threatening or long-term debilitating nature of the condition

The CHMP recommended extending the approved therapeutic indication for Nexavar to include the following indication:

'treatment of patients with progressive, locally advanced or metastatic, differentiated (papillary/follicular/Hürthle cell) thyroid carcinoma, refractory to radioactive iodine'.

This falls within the scope of the product's designated orphan conditions, which are: follicular and papillary thyroid cancers.

The COMP concluded that there had been no change in the seriousness of the conditions since the orphan designation in November 2013. Follicular and papillary thyroid cancers remain conditions that are debilitating in the long term and life threatening, particularly when the cancer does not respond to treatment and spreads to other parts of the body.

- Prevalence of the condition

The sponsor provided information on the prevalence of follicular and papillary thyroid cancers based on data from the 2008 Globocan database.

On the basis of the information provided by the sponsor and the knowledge of the COMP, the COMP concluded that the prevalence of follicular and papillary thyroid cancers remains below the ceiling for orphan designation, which is 5 people in 10,000. At the time of the review of the orphan designations, the prevalence of follicular thyroid cancer was still estimated to be between 0.2 and 0.9 people in 10,000, and the prevalence for papillary thyroid cancer was still between 1 and 3 people in 10,000. This is equivalent to a total of between 10,000 and 46,000 people in the EU for follicular thyroid cancer, and between 51,000 and 153,000 people in the EU for papillary thyroid cancer.

- Existence of other methods of treatment

At the time of the review of the orphan designation, the main treatment for follicular thyroid and papillary cancers in the EU was surgery to remove the thyroid. Therapy using radioactive iodine (^{131}I) to destroy thyroid cells was also used. Hormonal therapy was used as an additional treatment for preventing recurrence of the disease. In addition, the anticancer medicine doxorubicin was authorised for the treatment of follicular and papillary thyroid cancers in one EU Member State.

- Significant benefit of Nexavar

The COMP concluded that the claim of a significant benefit of Nexavar in follicular and papillary thyroid cancers is justified because of its demonstrated benefit in patients whose cancer has progressed or spread to other parts of the body and does not respond to radioactive iodine. These patients have no appropriate treatment options.

The COMP conclusions are based on data from a main study involving 419 patients with differentiated (papillary/follicular/Hürthle cell) thyroid cancer that had progressed or spread to other parts of the body and did not respond to radioactive iodine. The study showed that Nexavar increased the time that patients lived without their disease getting worse by an average of about 5 months more than placebo

[2] The maintenance of the orphan designation at time of marketing authorisation would, except in specific situations, give an orphan medicinal product 10 years of market exclusivity in the EU. This means that in the 10 years after its authorisation similar products with a comparable therapeutic indication cannot be placed on the market.

(a dummy treatment). Therefore, although other methods for the treatment of these conditions have been authorised in the EU, the COMP concluded that Nexavar is of significant benefit to patients affected by follicular and papillary thyroid cancer.

- Conclusions

Based on the data submitted and the scientific discussion within the COMP, the COMP considered that Nexavar still meets the criteria for designation as an orphan medicinal product and that it should remain in the Community Register of Orphan Medicinal Products.

The opinions not recommending the removal of Nexavar (Sorafenib tosylate) (EU/3/13/1199 and EU/3/13/1200) from the EC Register of Orphan Medicinal Products were adopted by consensus.

The draft public summary of the COMP opinion was adopted for publication on the EMA website.

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

5.2.1 Obinutuzumab for treatment of chronic lymphocytic leukaemia; Roche Registration Limited (EU/3/12/1054)

5.2.2 Masitinib mesylate for treatment of pancreatic cancer; AB Science (EU/3/09/684)

5.2.3 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)

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

5.3. On-going procedures

5.3.1 Autologous tumour-derived immunoglobulin idiotype coupled to keyhole limpet haemocyanin for treatment of follicular lymphoma; Biovest Europe Ltd (EU/3/06/394)

5.3.2 (1R,2R)-octanoic acid[2-(2',3'-dihydro-benzo[1,4] dioxin-6'-yl)-2-hydroxy-1-pyrrolidin-1-ylmethyl-ethyl]-amide-L-tartaric acid salt for treatment of Gaucher disease; Genzyme Europe BV (EU/3/07/514)

5.3.3 Mifepristone for treatment of hypercortisolism (Cushing's syndrome) of endogenous origin; FGK Representative Service GmbH (EU/3/11/925)

5.3.4 Ramucirumab for treatment of gastric cancer; Eli Lilly Nederland B.V. (EU/3/12/1004)

5.3.5 Human heterologous liver cells (for infusion); Cytonet GmbH&Co KG

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/821)

b) treatment of ornithine-transcarbamylase deficiency (EU/3/07/470)

c) treatment of citrullinaemia type 1 (EU/3/10/818)

d) treatment of hyperargininaemia (EU/3/10/819)

e) treatment of argininosuccinic aciduria (EU/3/10/820)

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

5.3.7 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. (EU/3/13/1115)

5.3.8 Tolvaptan for treatment of autosomal dominant polycystic kidney disease; Otsuka Pharmaceutical Europe Ltd (EU/3/13/1175)

5.3.9 Ketoconazole for treatment of Cushing's syndrome; Agenzia Industrie Difesa-Stabilimento Chimico Farmaceutico Militare (EU/3/12/1031)

5.3.10 Ketoconazole for treatment of Cushing's syndrome; Laboratoire HRA (EU/3/12/965)

5.3.11 Levofloxacin hemihydrate for treatment of cystic fibrosis; Aptalis Pharma SAS (EU/3/08/566)

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

5.3.13 Olaparib for treatment of ovarian cancer; AstraZeneca AB (EU/3/07/501)

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

5.3.15 Signifor (Pasireotide) for treatment of acromegaly; Novartis Europharm Limited (Type II variation) (EU/3/09/670)

5.3.16 L-Asparaginase for treatment of acute lymphoblastic leukaemia; medac Gesellschaft fuer klinische Spezialpraeparate mbH (EU/3/04/258)

5.3.17 Chimeric monoclonal antibody against GD2 for treatment of neuroblastoma; United Therapeutics Europe Ltd (EU/3/11/879)

5.3.18 Herpes simplex 1 virus-thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes for adjunctive treatment in haematopoietic cell transplantation; MolMed S.p.A. (EU/3/03/168)

6. Procedural aspects

6.1. European Medicines Agency Human Scientific Committees' Working Parties with Patients' and Consumers' Organisations (PCWP) and Healthcare Professionals' Organisations (HCPWP)

The Draft Agenda of the 3 June 2014 PCWP and HCPWP joint meeting EMA/136044/2014 was circulated for information.

7. Any other business

7.1. Informal CHMP/CAT/COMP meeting to be held on 28-29 October 2014 in Rome.

7.2. 5th presentation on the EMA move to 30 Churchill Place

7.3. EMA/COMP publications

- Significant Benefit
- Medical plausibility

7.4. Orphan conditions: Orphanet initiatives and views

A. Rath presented the topic.

Date of next COMP meeting: 10-12 June 2014

List of participants

Chair:

Bruno Sepodes

Vice-Chair:

Lesley Greene	Patient representative for Eurordis

COMP Members:

Irena Bradinova	Bulgaria
Kateřina Kubáčková	Czech Republic
Frauke Naumann-Winter	Germany
Vallo Tillmann	Estonia
Nikolaos Sypsas	Greece
Josep Torrent Farnell	Spain
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italy
Elena Kaisis	Cyprus
Dainis Krievins	Latvia
Henri Metz	Luxembourg
Judit Eggenhofer	Hungary
Albert Vincenti	Malta
Violeta Stoyanova-Beninska	The Netherlands
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Austria
Ana Corrêa-Nunes	Portugal
Flavia Saleh	Romania
Martin Možina	Slovenia
Zuzana Batová	Slovak Republic
Kerstin Westermark	Sweden
Daniel O'Connor	United Kingdom
Birthe Byskov Holm	Patient representative for Eurordis
Pauline Evers	Patient representative representing the European Genetic Alliances Network
Aikaterini Moraiti	EMA Representative

Observers:

Maria Mavris	Eurordis
Julian Isla	Dravet Syndrome Foundation

Visiting Expert:

Ana Rath	Inserm