EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11 December 2014
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Procedure Management and Business Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes of the 11-13 November 2014 meeting

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).

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1. Introduction

1.1 Adoption of the agenda, EMA/COMP/628196/2014

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 7-9 October 2014 EMA/COMP/575359/2014

The minutes were adopted with no amendments.

1.3 Conflicts of Interest

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

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Product for treatment of Huntington's disease - EMA/OD/114/14
[COMP Co-ordinator: 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:

- Medical plausibility

The medical plausibility of the proposal has not been supported with data confirming that treatment with the specific product as proposed for designation may result in beneficial effects on any aspect of the condition (cognitive, motor or behavioural) neither in relevant animal models nor in patients. The sponsor was requested to further elaborate on the clinical relevance of the endpoints studied in the preclinical experiments and present any further available data with the product as applied for designation.

- Significant benefit

The arguments on significant benefit are based on a new mechanism of action and the potentially improved efficacy in the condition. The sponsor was requested to specifically elaborate on the consequences of a novel mechanism and demonstrate any improved effects in relevant models of the condition.

With regards to safety, extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is necessary to justify safety arguments.

In the written response, and during an oral explanation before the Committee on 11 November 2014, the sponsor discussed that the mechanism of action of the product would be expected to improve the neural function by improving corticostriatal connectivity, enhancing output of both direct and indirect striatal pathways, and also by improving hippocampal plasticity. The sponsor also argued that, this product should have a more acceptable safety profile compared to authorised products based on data from other indications.

[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 COMP considered that in the absence of data in the specific indication as applied for designation it would be difficult to conclude on the claims made. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 November 2014, prior to final opinion.

2.1.2 Allogeneic bone marrow derived mesenchymal cells expanded ex vivo in synthetic media for prevention of graft-versus-host disease, Cell2B Advanced Therapeutics, SA - EMA/OD/163/14

[COMP Co-ordinator: 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 prevention of graft-versus-host disease, the sponsor was asked to further elaborate on the three clinical cases presented and particularly on:

  - the reasons for concluding that the proposed product enhances engraftment of the HSCT in these three cases and which, among the data provided, support this conclusion;
  - the clinical details, including follow-up, of the three cases and of any other available patients;
  - the clinical relevance of the occurrence of GvHD in one out of two mismatched HSCT to the proposed clinical use of the product.

The sponsor was also invited to present any additional available preclinical or clinical data supporting the medical plausibility. Whenever preclinical data are not available, the sponsor was invited to justify the reasons for not producing this type of data in support to the plausibility, including e.g. discussion on the use and limitations of models of the condition.

- Number of people affected

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

In this case the sponsor has provided estimates of the incidence/prevalence of GvHD rather than providing an estimate of the population at risk. As the product is proposed in preventive use, the estimated population at risk is expected to include all patients undergoing bone marrow/haematopoietic stem cell transplantation.

The sponsor was therefore invited to provide an estimate of the population at risk of GvHD.

- Significant benefit

In absence of an established medical plausibility the significant benefit is difficult to evaluate.

In the written response, and during an oral explanation before the Committee on 11 November 2014, the sponsor further supported the medical plausibility of the proposed product discussing literature data that indicate that MSC preventive use would result in lower occurrence of GvHD and of severe GvHD. Data from the literature also suggest a reduction in the occurrence of GvHD. This was considered sufficient by the COMP for supporting the medical plausibility of the product together with the three clinical case reports presented in the first submission. Significant benefit was considered

based on the different mechanism of action from the currently authorized treatments that offers the potential of a use in combination.

The sponsor also revised the calculations of the population at risk as requested based on rates of HSCT from 2012 European Bone Marrow Transplant data, and assuming a linear increase in the number of HSCT in the past three years.

The Committee agreed that the condition, graft-versus-host disease, is a distinct medical entity and meets the criteria for orphan designation.

The intention to prevent the condition with the medicinal product containing allogeneic bone marrow derived mesenchymal cells expanded ex vivo in synthetic media was considered justified based on preliminary clinical data showing low rates of occurrence of graft-versus-host disease with the proposed product.

The condition is chronically debilitating or life-threatening depending on the severity and the response to treatment with corticosteroids and other immunosuppressive agents. Severe intestinal inflammation with diarrhoea, abdominal pain, nausea and vomiting, skin rash and damage to the mucosa can occur. Severe infection can occur due to the immunosuppressive agents currently used for the treatment of the condition. Mortality from graft-versus-host disease can reach 100% in the severe forms not responding to immunosuppressive treatment.

The population of patients eligible for prevention of the condition was estimated to be less than 0.4 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of prevention of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing allogeneic bone marrow derived mesenchymal cells expanded ex vivo in synthetic media may be of significant benefit to the population at risk of developing the condition. The sponsor has provided preliminary clinical data that demonstrate a low rate of occurrence of graft-versus-host disease when the proposed product was co-administered with bone marrow transplantation from mismatched donors. The Committee considered that this constitutes a clinically relevant advantage for the patients at risk of the condition.

A positive opinion for allogeneic bone marrow derived mesenchymal cells expanded ex vivo in synthetic media, for treatment of graft-versus-host disease, was adopted by consensus.

2.1.3 Product for treatment of mantle cell lymphoma - EMA/OD/151/14

[COMP Co-ordinator: F. Naumann-Winter]

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

In order to justify the significant benefit the sponsor was invited to further discuss the relevance of the preclinical results obtained in the in vivo studies to the potential clinical use of the product vs. the currently authorized products for the condition, taking into account:

  - the lack of any positive control group reflecting the current standards of care;
  - the toxicity episodes leading to withdrawal of some subjects from the study and to the suspension of the treatment for a few days;

- the relevance of the *sc* administration to the expected administration and dosing in humans, in view of the absence of clinical experience at the present stage.

In the written response, and during an oral explanation before the Committee on 11 November 2014, the sponsor further elaborated on the preclinical studies performed and stated that at the time the experiments were made, there was no established standard of care for Mantle Cell Lymphoma. The COMP considered that it would be difficult to justify significant benefit without data with the proposed product that would allow a comparison to currently authorised treatments.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 12 November 2014, prior to final opinion.

2.1.4 Adeno-Associated Viral vector serotype rh.10 carrying the human N-sulfoglucosamine sulfohydrolase cDNA for treatment of Mucopolysaccharidosis type IIIA (Sanfilippo A syndrome), LYSOGENE - EMA/OD/164/14
[COMP Co-ordinator: 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:

- 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 Mucopolysaccharidosis type IIIA (Sanfilippo A syndrome), the sponsor was asked to elaborate on any further available endpoints studied in the preclinical models used, such as primary and secondary accumulation products (HS-derived oligosaccharides, GM3 and unesterified cholesterol) or any neurological assessments.

The sponsor was also invited to further elaborate on the rationale for the modification of the vector used.

In the written response, and during an oral explanation before the Committee on 11 November 2014, the sponsor elaborated on the design of the construct used in the proposed viral vector, and also bridged to other gene therapy products for the condition subject of this application.

The Committee agreed that the condition, mucopolysaccharidosis type IIIA (Sanfilippo A syndrome), 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 10 carrying the human N-sulfoglucosamine sulfohydrolase cDNA was considered justified based on results in preclinical models showing expression of the missing enzyme in the brain.

The condition is chronically debilitating and life-threatening, in particular due to neurologic involvement leading to poor development of language and motor skills, hyperactivity, overall delay in development and reduction of life expectancy.

The condition was estimated to be affecting less than 0.1 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.

A positive opinion for adeno-associated viral vector serotype 10 carrying the human N-sulfoglucosamine sulfohydrolase cDNA, for treatment of mucopolysaccharidosis type IIIA (Sanfilippo A syndrome), was adopted by consensus.

2.1.5 Heat killed whole cell Mycobacterium obuense for treatment of pancreatic cancer, Immodulon Therapeutics Ltd - EMA/OD/143/14
[COMP Co-ordinator: K. Kubáčková]

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 pancreatic cancer, the sponsor was asked to further elaborate on:

  - the clinical relevance of a polyclonal stimulation of T lymphocytes, such as the one demonstrated with the proposed product, for the intended specific use in pancreatic cancer;
  - the lack of conclusive results from similar approaches such as the stimulation with BCG;
  - the results from the preclinical study, showing no effect on survival when the product was used alone or in combination with gemcitabine. For this study the sponsor was also invited to clarify how metastatisation was defined.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit, and in particular the suggested use of the product in combination with currently authorized products, taking into account the lack of effect in the preclinical models on survival when the product was used in combination with gemcitabine.

The sponsor was also invited to present any results available from the randomised, open-label, proof-of-concept, Phase II trial where the recruitment was concluded in July 2013.

In the written response, and during an oral explanation before the Committee on 12 November 2014, the sponsor further discussed the immunology of the proposed product and in particular the effects of the product on the innate and acquired immune system. The sponsor also discussed the clinical data from a proof of concept Phase II trial comparing gemcitabine with and without the product in patients with advanced pancreatic cancer.

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

The intention to treat the condition with the medicinal product containing heat-killed *Mycobacterium obuense* (whole cell) was considered justified based on preclinical data showing reduction of tumour size and of metastasis with the proposed product.

The condition is life-threatening and chronically debilitating due to early dissemination of the tumour to distant sites including brain, bone, soft tissues, and lungs. The condition has a 5 year survival rate of 6%.

The condition was estimated to be affecting approximately 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 heat-killed *Mycobacterium obuense* (whole cell) may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing improved clinical response in patients affected by pancreatic cancer when the product is used in combination with currently authorized products. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion containing heat-killed *Mycobacterium obuense* (whole cell) for treatment of pancreatic cancer, was adopted by consensus.

2.1.6 Exisulind for treatment of familial cerebral cavernous malformations, Firc Institute of Molecular Oncology (IFOM) - EMA/OD/161/14
[COMP Co-ordinator: 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 familial cerebral cavernous malformations, the sponsor was asked to further elaborate on:

  - the rationale and relevance of the preclinical CCM3 -/- model used for the treatment of familial cerebral cavernous malformations that is caused by any of the three genes CCM1, CCM2, CCM3, and the interpretation of the results obtained in the experiments.

- Number of people affected

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 based their prevalence calculation on the available literature on both, spontaneous and familial forms of cerebral cavernous malformations, and reports from genetic databases. Given the wide range of the proposed prevalence and the substantial uncertainty about many of the assumptions regarding the prevalence, the sponsor was asked to recalculate the prevalence estimate and perform a sensitivity analysis of the reported calculations.

In the written response, and during an oral explanation before the Committee on 12 November 2014, the sponsor justified the relevance of the CCM3 -/- model as a preclinical model of the disease, highlighting that all 3 available models, CCM1 -/-, CCM2 -/-, and CCM 3 -/- show an identical phenotype, caused by endothelial-to-mesenchymal transition in the brain, and can therefore all be considered relevant models of the condition. Moreover, the sponsor also proposed a revised prevalence calculation based on the available literature, including a sensitivity analysis, and proposes a prevalence estimate of 0.4 to 3 in 10,000.

The Committee agreed that the condition, familial cerebral cavernous malformations, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing exisulind was considered justified based on preclinical data in relevant models of the condition showing that the proposed product reduces the burden of vascular malformations in the central nervous system.

The condition is chronically debilitating due to focal seizures and neurological deficits determined by the localisation of the lesion, such as weakness of arms or legs, headache, vision impairment, memory and attention to problems, and life-threatening due to severe brain haemorrhage.

The condition was estimated to be affecting not more than 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 exisulind, for treatment of familial cerebral cavernous malformations, was adopted by consensus.

2.1.7 Product for treatment of acute myeloid leukaemia - EMA/OD/156/14

[COMP Co-ordinator: K. Kubáčková]

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 acute myeloid leukaemia, the sponsor was asked to further elaborate on:

  - the results obtained in vitro on AML cell lines from patients;
  - the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the condition as proposed for designation.

In the absence of data with the specific product in a specific (in vivo) model of the proposed condition as applied for designation, the intention to treat cannot be considered justified.

- Significant benefit

The sponsor proposes an alternative mode of action which may offer a clinically relevant advantage of improved efficacy over current therapies.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from any preclinical or clinical studies to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 12 November 2014, the sponsor elaborated on the proposed mechanism of action, discussed some further ex-vivo assays, and discussed the anticipated effects versus other existing therapies, but did not provide further data in vivo or in preliminary clinical settings. The COMP considered that in absence of these data, it would be difficult to consider the justification of medical plausibility and significant benefit.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 November 2014, prior to final opinion.

2.1.8 Product for treatment of myasthenia gravis- EMA/OD/119/14

[COMP Co-ordinator: 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 myasthenia gravis, the sponsor was asked to further elaborate on:

  - the proposed mechanism of action, by providing any available data to document the argued induction of apoptosis specifically in cells involved in immune response against the acetylcholine receptor;
  - the preventive settings of the preclinical model used for the purpose of medical plausibility, and the relevance of this model for the treatment of the condition;
  - any further available data in either relevant models of the proposed condition or in patients affected by the condition.

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the available preclinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 12 November 2014, the sponsor discussed the available preclinical data and with regards to the proof of concept in vivo study the sponsor provided some additional data in curative settings. With regards to the significant benefit, no data are presented but the sponsor expected a clinically relevant advantage based on the novel mechanism of action of the product. The COMP considered that it would be difficult to justify the significant benefit in the absence of data.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 13 November 2014, prior to final opinion.

2.1.9 Single chain urokinase plasminogen activator for treatment of pleural infection, Coté Orphan Consulting UK Limited - EMA/OD/125/14
[COMP Co-ordinator: S. Thorsteinsson]

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

Pleural infection should be justified as a distinct medical entity or a valid subset, for the purposes of orphan medicinal product designation. The sponsor's attention was drawn to the Orphan regulations and guidelines to clarify this (especially guideline ENTR/6283/00, and the "Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation").

Pleural infection is described as a stage of infection of the pleural space rather than a distinct condition or a valid subset, see e.g. the British Thoracic Society pleural disease guideline 2010: *"….Most forms of*

pleural infection represent a progressive process that transforms a 'simple' self-resolving parapneumonic pleural effusion into a 'complicated' multiloculated fibrinopurulent collection associated with clinical and/or biochemical features of sepsis".

The sponsor was therefore invited to justify on which basis the proposed condition should be considered a distinct medical entity or a valid subset rather than a stage of infections of the pleural space.

- Number of people affected

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 was asked to justify the choice of the sources selected for the estimation of the incidence of the condition, since it appears that most of the cited articles include only patients below 18 years of age.

The sponsor was asked to therefore describe and justify the methodology used for the prevalence calculation, and in particular the scarcity of the references provided in adult population versus paediatric, and the justifications for assuming a similar incidence of the condition in these populations. In this respect the sponsor was also invited to better clarify which population(s) the final estimated incidence is based on.

In addition, given the substantial uncertainty about many of the assumptions regarding the incidence, the sponsor was asked to perform a sensitivity analysis of the reported calculations.

The sponsor was also reminded that should the proposed indication be revised, the estimated incidence should be amended accordingly.

- Significant benefit

A number of antibiotics are authorized in the European Union for the treatment of pleural infection.

The sponsor was invited to discuss the significant benefit of the proposed product in relation to the standard of care, including antibiotics.

In the written response, and during an oral explanation before the Committee on 12 November 2014, the sponsor asked for revising the condition to "treatment of empyema". The sponsor argued that the characteristics of empyema, such as the fibrinopurulent parapneumonic fluid that is often not free floating (chiefly due to fibrin-walled loculations); a pH less than 7.2; glucose less than 35 mg/dL; lactate dehydrogenase greater than 1000 IU/L; and a positive Gram stain or bacterial culture make of empyema a distinct medical entity.

For a condition to be considered a distinct medical entity in the orphan regulation in the EU such condition needs to "generally be defined in terms of their specific characteristics, e.g. pathophysiological, histopathological, clinical characteristics" (General considerations, point a), Guideline ENTR/6283/00 Rev 4), and "Different degrees of severity or stages of a disease would generally not be considered as distinct conditions" (General considerations, point c), Guideline ENTR/6283/00 Rev 4). When the proposed condition was to be considered as a valid subset (it is not clear from the different changes proposed by the sponsor whether it should be considered a subset of pleural infection), the subset is assumed to be valid if "patients in that subset present distinct and unique evaluable characteristic(s) with a plausible link to the condition and if such characteristics are essential for the medicinal product to carry out its action. In particular, the pathophysiological characteristics associated with this subset should be closely linked to the pharmacological action of the

medicinal product in such a way that the absence of these characteristics will render the product ineffective in the rest of the population suffering from the condition."

In this case the COMP was of the opinion that the fact that empyema is characterized by non free-floating fluid may support considering it a distinct medical entity, for this application.

The COMP also accepted that the data from the Danish study together with the studies on children can be considered sufficient to support the incidence of empyema proposed by the sponsor and concluded with an estimate of approximately 1.3 in 10,000 in the EU.

The significant benefit was based on the different mechanism of action of the proposed product versus the currently authorized methods for the treatment of empyema that include antibiotic treatment and surgery. The proposed product, targeting the formation of fibrin adherences offers the potential of being used in combination with the currently authorized treatments for empyema.

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

The intention to treat the condition with the medicinal product containing single-chain urokinase plasminogen activator was considered justified based on preclinical models of the disease showing reduction of fibrin adhesions and clearance of fibrin deposits.

The condition is life-threatening in cases not responding to treatment, with mortality up to 20%. The condition can be chronically debilitating due to the formation of pleural adhesions that can potentially limit lung expansion.

The condition was estimated to be affecting approximately 1.3 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 single-chain urokinase plasminogen activator may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the product reduces the formation of fibrin adhesions, therefore it targets the condition in a way complementary to the currently authorized treatments. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by pleural empyema.

A positive opinion for single-chain urokinase plasminogen activator, for treatment of pleural empyema, was adopted by consensus.

2.1.10 Sodium ascorbate and menadione sodium bisulfite for treatment of autosomal dominant polycystic kidney disease, JJGConsultancy Ltd - EMA/OD/042/14.

A negative opinion on orphan medicinal product designation for Sodium ascorbate and menadione sodium bisulfite, for treatment of autosomal dominant polycystic kidney disease, was adopted by consensus via written procedure on 21 July 2014. The COMP has been informed that the sponsor has not appealed the opinion.

2.2. For discussion / preparation for an opinion

2.2.1 ((E)-1-(4'-chlorophenyl)-3-(4-hydroxy-3-metoxyphenyl)prop-2-en-1-one) for treatment of WHIM Syndrome, Centre National de la Recherche Scientifique (CNRS) - EMA/OD/142/14
[COMP Co-ordinator: F. Saleh]

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

The intention to treat the condition with the medicinal product containing ((E)-1-(4'-chlorophenyl)-3-(4-hydroxy-3-metoxyphenyl)prop-2-en-1-one) was considered justified based on pre-clinical data using a valid model of the condition showing a reversal of circulating pan leukopenia.

The condition is life-threatening due to the risk of developing cancer which is a significant cause of premature mortality and chronically debilitating due to patients suffering from recurrent infections from early childhood as well as numerous warts on hands, feet and trunk.

The condition was estimated to be affecting approximately 0.002 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 ((E)-1-(4'-chlorophenyl)-3-(4-hydroxy-3-metoxyphenyl)prop-2-en-1-one), for treatment of WHIM syndrome was adopted by consensus.

2.2.2 (1S,4R,5R,7S)-3,4-dibenzyl-2-oxo-6,8-dioxa-3-azabyciclo[3.2.1]octane-7-carboxylic acid-L-lysine for treatment of neurotrophic keratitis, MIMETECH S.r.l. - EMA/OD/185/14
[COMP Co-ordinator: J. Torrent-Farnell]

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

The intention to treat the condition with the medicinal product containing (1S,4R,5R,7S)-3,4-dibenzyl-2-oxo-6,8-dioxa-3-azabyciclo[3.2.1]octane-7-carboxylic acid-L-lysine was considered justified based on preclinical data showing reduction of corneal damage with the proposed product.

The condition is chronically debilitating due to progressive damage of corneal epithelium and stroma leading to loss of vision. Corneal ulceration, infection and perforation can also occur.

The condition was estimated to be affecting less than 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 1S,4R,5R,7S)-3,4-dibenzyl-2-oxo-6,8-dioxa-3-azabyciclo[3.2.1]octane-7-carboxylic acid-L-lysine, for treatment of neurotrophic keratitis, was adopted by consensus.

2.2.3 1-(2-isopropoxyethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d] pyrimidin-4-one for treatment of multiple system atrophy, AstraZeneca AB - EMA/OD/193/14
[COMP Co-ordinator: D. O'Connor]

The Committee agreed that the condition, multiple system atrophy, 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-isopropoxyethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one was considered justified based on a valid in vivo pre-clinical model of the condition which showed a potential for neuronal protection.

The condition is life-threatening due to pulmonary embolism, apnea, and infection and chronically debilitating due to a progressive loss of motor skills.

The condition was estimated to be affecting approximately 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 1-(2-isopropoxyethyl)-2-thioxo-1,2,3,5-tetrahydro-pyrrolo[3,2-d]pyrimidin-4-one, for treatment of multiple system atrophy, was adopted by consensus.

2.2.4 2-hydroxymethyl-2-methoxymethyl-1-azabicyclo[2,2,2]octan-3-one for treatment of ovarian cancer, Aprea AB - EMA/OD/157/14
[COMP Co-ordinator: B. Bloechl-Daum]

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

The intention to treat the condition with the medicinal product containing 2-hydroxymethyl-2-methoxymethyl-1-azabicyclo[2,2,2]octan-3-one was considered justified based on the synergic effects observed in the preclinical model of ovarian cancer when the medicinal product was used in combination with cisplatin and carboplatin and also on the preliminary clinical results observed in patients with platinum sensitive recurrent p53 mutated high-grade serous ovarian cancer.

The condition is chronically debilitating in particular due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years.

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 2-hydroxymethyl-2-methoxymethyl-1-azabicyclo[2,2,2]octan-3-one may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data in a model of the condition, supporting a synergistic effect in tumour growth when used in combination with cisplatin. The sponsor also provided preliminary clinical data showing a reduction in the level of CA-125 and tumour size in treated patients. The improved effects when added on top of other authorised products may justify the assumption of improved efficacy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 2-hydroxymethyl-2-methoxymethyl-1-azabicyclo[2,2,2]octan-3-one, for treatment of ovarian cancer, was adopted by consensus.

2.2.5 5,5'-(4-(trifluromethyl)benzylazanediyl)bis(methylene)diquinolin-8-ol for treatment of glioma, Prof. Olivier Blin - EMA/OD/200/14
[COMP Co-ordinator: K. Kubáčková]

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

The intention to treat the condition with the medicinal product containing 5,5'-(4-(trifluromethyl)benzylazanediyl)bis(methylene)diquinolin-8-ol was considered justified based on preliminary pre-clinical in vivo data showing improved survival.

The condition is chronically debilitating due to symptoms caused by compression by the tumour on the surrounding brain tissue. Such symptoms include headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment. It is also life-threatening, with poor 5-year survival of less than 5% for glioblastoma multiforme patients.

The condition was estimated to be affecting approximately 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 5,5'-(4-(trifluromethyl)benzylazanediyl)bis(methylene)diquinolin-8-ol (Chemical) may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo data that demonstrate improved survival when compared with temozolomide. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 5,5'-(4-(trifluromethyl)benzylazanediyl)bis(methylene)diquinolin-8-ol, for treatment of glioma, was adopted by consensus.

2.2.6 5-[8-methyl-9-(1-methylethyl)-2-(4-morpholinyl)-9H-purin-6-yl]-2-pyrimidinamine for treatment of malignant mesothelioma, TMC Pharma Services Ltd - EMA/OD/168/14
[COMP Co-ordinator: K. Kubáčková]

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

The intention to treat the condition with the medicinal product containing 5-[8-methyl-9-(1-methylethyl)-2-(4-morpholinyl)-9H-purin-6-yl]-2-pyrimidinamine was considered justified based on data in preclinical models of the condition showing inhibition of tumour growth.

The condition is life-threatening with a median survival of approximately 12 months.

The condition was estimated to be affecting less than 0.5 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 5-[8-methyl-9-(1-methylethyl)-2-(4-morpholinyl)-9H-purin-6-yl]-2-pyrimidinamine may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing an improved effect on tumour growth compared to pemetrexed in combination with cisplatin. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 5-[8-methyl-9-(1-methylethyl)-2-(4-morpholinyl)-9H-purin-6-yl]-2-pyrimidinamine, for treatment of malignant mesothelioma, was adopted by consensus.

2.2.7 5-bromo-N-(prop-2-yn-1-yl)-2-(1H-1,2,4-triazol-1-yl) pyrimidine-4,6-diamine for treatment of Huntington's disease, Palobiofarma S.L. - EMA/OD/169/14
[COMP Co-ordinator: V. Stoyanova]

The Committee agreed that the condition, Huntington'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 5-bromo-N-(prop-2-yn-1-yl)-2-(1H-1,2,4-triazol-1-yl) pyrimidine-4,6-diamine was considered justified based on preclinical data showing improvements in motor and cognitive outcomes in a preclinical setting.

The condition is chronically debilitating due to progressive motor dysfunction, severe behavioural and cognitive disturbances, and life-threatening with a median survival time reported in the range of 15 to 18 years after onset.

The condition was estimated to be affecting approximately 1 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 5-bromo-N-(prop-2-yn-1-yl)-2-(1H-1,2,4-triazol-1-yl) pyrimidine-4,6-diamine may be of significant benefit to those affected by the condition. The sponsor has provided data in a preclinical model of the condition that demonstrate beneficial effects of the administration of the product with regards to cognitive endpoints and motor function. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 5-bromo-N-(prop-2-yn-1-yl)-2-(1H-1,2,4-triazol-1-yl)pyrimidine-4,6-diamine, for treatment of Huntington's disease, was adopted by consensus.

2.2.8 Product for treatment of the Adult T-cell leukemia/lymphoma - EMA/OD/203/14
[COMP Co-ordinator: J. Torrent-Farnell]

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 the adult T-cell leukaemia/lymphoma, the sponsor was asked to further elaborate on:

  - the lack of preclinical and /or clinical data showing any type of anti-tumour effect of the proposed product;
  - the relevance of the results obtained *in vitro* showing immunogenic response to the clinical translation in the proposed condition;
  - the relevance of using two different serotypes to the assumed clinical efficacy of the product.

- Significant benefit

In absence of an established medical plausibility the significant benefit of the product cannot be assessed. Therefore sponsor is invited to provide any available data to support the medical plausibility.

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 December meeting.

2.2.9 Product for treatment of the adult T-cell leukemia/lymphoma - EMA/OD/204/14

[COMP Co-ordinator: J. Torrent-Farnell]

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 the adult T-cell leukaemia/lymphoma, the sponsor was asked to further elaborate on:

  - the lack of preclinical and /or clinical data showing any type of anti-tumour effect of the proposed product;
  - the relevance of the results obtained *in vitro* showing immunogenic response to the clinical translation in the proposed condition;
  - the relevance of using two different serotypes to the assumed clinical efficacy of the product.

- Significant benefit

In absence of an established medical plausibility the significant benefit of the product cannot be assessed. Therefore sponsor is invited to provide any available data to support the medical plausibility.

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 December meeting.

2.2.10 Product for treatment of placental insufficiency - EMA/OD/198/14

[COMP Co-ordinator: V. Tillmann]

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

- Intention to diagnose, prevent or treat

Placental insufficiency should be further justified as a distinct medical entity, for the purposes of orphan medicinal product designation. The sponsor's attention was drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

- Number of people affected

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 was asked to re-calculate the epidemiological indices based on relevant epidemiological studies and registers for the proposed orphan condition, and given the substantial uncertainty about many of the assumptions regarding the number of people affected, not least the uncertainty about the definition of the condition, the sponsor was asked to perform a sensitivity analysis of the reported calculations.

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

2.2.11 Adenovirus serotype 5 containing partial E1A deletion and an integrin-binding domain for treatment of glioma, Alan Boyd Consultants Ltd - EMA/OD/176/14
[COMP Co-ordinator: K. Kubáčková]

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

The intention to treat the condition with the medicinal product containing adenovirus serotype 5 containing partial E1A deletion and an integrin-binding domain was considered justified based on preclinical data in models of the condition showing improved survival and preliminary clinical data showing responses in treated patients.

The condition is chronically debilitating due to symptoms caused by compression by the tumour on the surrounding brain tissue including headache, anorexia, nausea, vomiting, seizures, neurological deficits, personality and cognitive impairment, and life-threatening with 5-year survival of less than 5% for glioblastoma multiforme patients.

The condition was estimated to be affecting approximately 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 adenovirus serotype 5 containing partial E1A deletion and an integrin-binding domain may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that show clinically relevant responses in patients with glioma relapsing after treatment with the standard of care. The Committee considered that this constitutes a clinically relevant advantage

A positive opinion for adenovirus serotype 5 containing partial E1A deletion and an integrin-binding domain, for treatment of glioma, was adopted by consensus.

2.2.12 Adipose-derived adult mesenchymal stem cells of allogenic origin contained in a fibrin-based bioengineered dermis for treatment of epidermolysis bullosa, Biodan Yelah S.L. - EMA/OD/197/14
[COMP Co-ordinator: F. Naumann-Winter]

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

The intention to treat the condition with the medicinal product containing allogeneic adipose-derived adult mesenchymal stem cells contained in a fibrin-based bioengineered dermis was considered justified based on reduction of wound size, and increased re-epithelization with the proposed product in preclinical models of the condition.

The condition is life-threatening and chronically debilitating due to recurrent skin blistering leading to disabling physical deformities and to severe and painful skin infections that can lead to the development of sepsis, and to a high susceptibility to squamous cell carcinoma.

The condition was estimated to be affecting less than 0.8 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 allogeneic adipose-derived adult mesenchymal stem cells contained in a fibrin-based bioengineered dermis, for treatment of epidermolysis bullosa, was adopted by consensus.

2.2.13 Product for treatment of systemic sclerosis - EMA/OD/207/14
[COMP Co-ordinator: J. Torrent-Farnell]

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 the treatment of systemic sclerosis, the sponsor was asked to further elaborate on:

  - the scientific rationale of using this product in the treatment of systemic sclerosis taking into account the immunomodulatory activity profile of MSC in relation to the specific immunologic (autoimmune) pattern in systemic sclerosis;
  - the overall lack of data (in the literature and/or sponsor-generated) supporting the medical plausibility of the proposed product in systemic sclerosis;
  - the results of the only small case series in systemic sclerosis that have been defined as “non conclusive”.

- Significant benefit

The sponsor was invited to present and discuss any available preclinical or clinical data supporting the significant benefit of the proposed product in comparison to what is currently authorized for the treatment of systemic sclerosis.

In absence of a valid medical plausibility the significant benefit of the proposed product cannot be assessed.

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 December meeting.

2.2.14 Allogeneic CD34+ cells expanded ex-vivo with an aryl hydrocarbon receptor antagonist for treatment of B-lymphoblastic leukaemia/lymphoma, Novartis Europharm Limited - EMA/OD/120/14
[COMP Co-ordinator: B. Bloechl-Daum]

Following review of the application by the Committee, it was agreed to broaden the indication to treatment of acute lymphoblastic leukaemia.

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

The intention to treat the condition with the medicinal product containing allogeneic CD34+ cells expanded ex vivo with an aryl hydrocarbon receptor antagonist was considered justified based on preclinical data and preliminary clinical data.

The condition is chronically debilitating and life-threatening depending on the response to treatment, with acute leukemic forms being fatal in a few weeks if left untreated. The main manifestations of the disease such as persistent fever, infections, anaemia, fatigue, breathlessness, bone and joint pain, are linked to invasion by the tumour cells of the bloodstream, the bone marrow and/or the lymph nodes and other lymphatic organs, resulting in lack of normal blood cells, bone marrow failure, and specific organ damage.

The condition was estimated to be affecting approximately 1.3 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 allogeneic CD34+ cells expanded ex vivo with an aryl hydrocarbon receptor antagonist may be of significant benefit to those affected by the condition. The sponsor has provided preclinical and preliminary clinical data that show shortened time to neutrophil recovery. Acceleration of neutrophil recovery may improve clinical outcomes within the first few weeks after UCB transplantation by reducing acute infections.

The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for allogeneic CD34+ cells expanded ex vivo with an aryl hydrocarbon receptor antagonist, for treatment of acute lymphoblastic leukaemia, was adopted by consensus.

2.2.15 Product for treatment of acute myeloid leukaemia - EMA/OD/188/14
[COMP Co-ordinator: F. Naumann-Winter]

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 acute myeloid leukaemia, the sponsor was asked to further elaborate on any data with the specific product as applied for designation in AML-specific situations.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results presented to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

The sponsor was asked to detail the results of any clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of these patients. In the absence of any data with the product as applied for in the condition the significant benefit cannot be established.

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 December meeting.

2.2.16 Allogeneic ex vivo-generated natural killer cells from CD34+ umbilical cord blood progenitor cells for treatment of acute myeloid leukaemia, IPD-Therapeutics BV - EMA/OD/175/14
[COMP Co-ordinator: B. Dembowska-Bagińska]

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

The intention to treat the condition with the medicinal product containing allogeneic ex vivo-generated natural killer cells from CD34+ umbilical cord blood progenitor cells was considered justified based on a preclinical model where increased survival was shown when the product was administered together with IL-15.

The condition is life-threatening and chronically debilitating 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 condition was estimated to be affecting approximately 1 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 allogeneic ex vivo-generated natural killer cells from CD34+ umbilical cord blood progenitor cells may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrated that the product could increase efficacy when used with other therapies.

The Committee considered that this constitutes a clinically relevant advantage for the patient population affected by the condition.

A positive opinion for allogeneic ex vivo-generated natural killer cells from CD34+ umbilical cord blood progenitor cells, for treatment of acute myeloid leukaemia, was adopted by consensus.

2.2.17 Amikacin sulfate for infections in cystic fibrosis patients, PlumeStars s.r.l. - EMA/OD/177/14
[COMP Co-ordinator: J. Eggenhofer]

Following review of the application by the Committee, it was agreed to rename the indication to "treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis".

The Committee agreed that the condition, *Pseudomonas aeruginosa* lung infection in 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 amikacin sulfate was considered justified based on the current authorised use of amikacin in the standard of care for the treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis and from preclinical data showing equivalent bactericidal activity of the proposed product to the commercially available formulation of amikacin.

The condition is chronically debilitating due to the chronic inflammation of the infected airways leading to cystic fibrosis exacerbations and progressive damage of the airway walls. The condition is life-threatening due to the development of bronchiectasis in the chronically inflamed airways, with possible erosion of the bronchial wall and haemoptysis due to rupture of pulmonary vessels.

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 amikacin sulfate may be of significant benefit to those affected by the condition. A formulation for inhalation allows use of the product in outpatient setting versus the current in-hospital only use, which could constitute a major contribution to patient care.

A positive opinion for amikacin sulfate, for treatment of *Pseudomonas aeruginosa* lung infection in cystic fibrosis, was adopted by consensus.

2.2.18 Product for treatment of glioma - EMA/OD/181/14
[COMP Co-ordinator: F. Naumann-Winter]

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 glioma, the sponsor was asked to further elaborate on:

  - the relevance of the results obtained in the preclinical model;
  - any further available data with the product as proposed for designation in models of the condition, or in patients affected by the condition.

- Significant benefit

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

The sponsor was invited to provide and discuss any data with the product in relevant models of the condition or in preliminary clinical settings that may justify a clinically relevant advantage compared to the authorised treatment methods for the 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 December meeting.

2.2.19 Autologous collagen type II-specific regulatory T cells for treatment of non-infectious uveitis, TxCell - EMA/OD/195/14
[COMP Co-ordinator: K. Westermark]

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

The intention to treat the proposed condition with the medicinal product containing autologous collagen type II-specific regulatory T cells was considered justified based on preclinical data in a valid animal model.

The condition is chronically debilitating due to visual loss.

The condition was estimated to be affecting approximately 4.8 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 autologous collagen type II-specific regulatory T cells may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate that the proposed medicinal product could have improved efficacy. A further advantage could be a reduction of the use of corticosteroids. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous collagen type II-specific regulatory T cells, for treatment of non-infectious uveitis, was adopted by consensus.

2.2.20 Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3 zeta chimeric antigen receptor for treatment of diffuse large B cell lymphoma, Kite Pharma UK, Ltd - EMA/OD/171/14
[COMP Co-ordinator: F. Naumann-Winter]

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

The intention to treat the condition with the medicinal product containing autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3 zeta chimeric antigen receptor was considered justified based on preliminary clinical data showing anti-cancer activity in patients with refractory disease.

The condition is chronically debilitating due to involvement of single or multiple nodal or extranodal sites, including the gastrointestinal tract and bone marrow and life-threatening with 5-year survival rates reported as low as approximately one in four patients for the high risk group.

The condition was estimated to be affecting approximately 2.4 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 autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3 zeta chimeric antigen receptor may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data showing a favourable response in patients with progressive disease who are refractory to previous treatments. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3 zeta chimeric antigen receptor, for treatment of diffuse large B cell lymphoma, was adopted by consensus.

2.2.21 Benserazide hydrochloride for treatment of beta-thalassemia intermedia and major, Isabelle Ramirez - EMA/OD/189/14
[COMP Co-ordinator: A. Lorence]

The Committee agreed that the condition, beta-thalassaemia intermedia and major, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing benserazide hydrochloride was considered justified based on preclinical data demonstrating that the product induced foetal haemoglobin (HbF) and subsequently increased total haemoglobin levels in relevant models of the disease.

The condition is life-threatening and chronically debilitating due to the severe anaemia, the need for blood transfusions, and the complications related to these, in particular in beta-thalassaemia major patients.

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

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing benserazide hydrochloride may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data in relevant models of the disease that demonstrate that the product was capable of increasing total haemoglobin levels by inducing foetal haemoglobin (HbF). The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for benserazide hydrochloride, for treatment of beta-thalassaemia intermedia and major, was adopted by consensus.

2.2.22 Bevacizumab for treatment of hereditary haemorrhagic telangiectasia, Dr Sophie Dupuis-Girod - EMA/OD/167/14
[COMP Co-ordinator: K. Westermark]

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

The intention to treat the condition with the medicinal product containing bevacizumab was considered justified based on data in relevant preclinical models and preliminary data in patients with the condition showing improvements in epistaxis.

The condition is chronically debilitating and life threatening, especially due to haemorrhagic, shunting and space occupying complications of mucocutaneous and visceral arterio-venous malformations.

The condition was estimated to be affecting not more than 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 bevacizumab, for treatment of hereditary haemorrhagic telangiectasia, was adopted by consensus.

2.2.23 Chenodeoxycholic acid for treatment of inborn errors of primary bile acid synthesis, Sigma-Tau Pharma Ltd - EMA/OD/196/14
[COMP Co-ordinator: J. Torrent-Farnell]

The Committee agreed that the condition, inborn errors in primary bile acid synthesis, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing chenodeoxycholic acid was considered justified based on evidence from the published literature that the product improves liver function, reduces abnormal bile in serum and urine, and reduces disease-specific symptoms in patients.

The condition is chronically debilitating due to progressive neurological decline, fat malabsorption and fat-soluble vitamin deficiencies, and life-threatening in particular due to the development of liver cirrhosis and liver failure.

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.

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 chenodeoxycholic acid may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that chenodeoxycholic acid could be better than authorised medicines to treat the condition and prevent further progression of the disease, in particular due to its inhibitory action on the rate-limiting enzymes in cholesterol homeostasis. The product can also be effective in inborn errors in primary bile acid synthesis that are not amenable to cholic acid treatment. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for chenodeoxycholic acid, for treatment of inborn errors in primary bile acid synthesis, was adopted by consensus.

2.2.24 Product for treatment of neuroblastoma - EMA/OD/199/14
[COMP Co-ordinator: B. Dembowska-Bagińska]

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 neuroblastoma, the sponsor was asked to further elaborate on:

  - The specification of the final product and on any available data with the final product as applied for designation.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on any available data with the product as applied for designation. In the absence of data with the product as applied for designation significant benefit cannot be assessed.

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 December meeting.

2.2.25 Product for treatment of pancreatic cancer - EMA/OD/178/14
[COMP Co-ordinator: B. Bloechl-Daum]

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 pancreatic cancer, the sponsor was asked to further elaborate on:

- details on the proposed product, in particular the rationale for the proposed formulation in capsules and pharmacokinetics of both, the active substance and the capsules;
- details on the clinical studies, in particular patients' characteristics and treatment protocols.

- Significant benefit

The arguments on significant benefit are based on a potential improved efficacy in the condition.

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on:

- the comparison of the results for the phase I/II studies with the current standard of care for a similar population in the context of current European guidelines.

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 December meeting.

2.2.26 Edaravone for treatment of amyotrophic lateral sclerosis, Treeway B.V. - EMA/OD/184/14
[COMP Co-ordinator: V. Stoyanova]

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

The intention to treat the condition with the medicinal product containing edaravone was considered justified based on pre-clinical in vivo data using a valid animal model of the condition and preliminary clinical data in patients with ALS.

The condition is life-threatening due to a median survival time from onset to death of 39 months.

The condition was estimated to be affecting approximately 1 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 edaravone may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical in vivo and clinical data showing favourable effects in relevant endpoints in the condition when edaravone is used in combination with riluzole. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for edaravone, for treatment of amyotrophic lateral sclerosis, was adopted by consensus.

2.2.27 Product for treatment of Aicardi-Goutières syndrome - EMA/OD/206/14
[COMP Co-ordinator: G. Capovilla]

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 Aicardi-Goutières syndrome, the sponsor was asked to further elaborate on:

- how the in vivo model supports the medical plausibility in all AGS types;
- what the difference is in the pathogenic mechanism between AGS types 1-5 and AGS6-7, and why the latter could not be included in the OD;
- how the treatment can practically be given in the time window required to halt the neurological damage;
- whether there is a risk that the proposed treatment strategy (treatment only in the initial stages of the disease) does not abrogate but simply postpone the neurological disease process to a later time point/older age;
- whether the product crosses the blood–brain barrier (if this is indeed required).

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 December meeting.

2.2.28 Product for treatment of cystinosis - EMA/OD/202/14
[COMP Co-ordinator: A. Magrelli]

Having reviewed the sponsor's application, the COMP considered that based on preclinical data in a relevant preclinical model of the condition the medical plausibility may be considered acceptable. It was also considered the condition is chronically debilitating and life threatening due to development of renal failure, and was estimated to be affecting approximately 0.1 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 committee considered that a major contribution to patient care may be eventually acceptable, mainly on the basis of an improved administration scheme.

Having reviewed the sponsor's application, the COMP considered that the application could be acceptable but the sponsor withdrew the application prior to adoption of final opinion by the COMP.

2.2.29 Genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor for treatment of malignant mesothelioma, Oncos Therapeutics Oy - EMA/OD/180/14
[COMP Co-ordinator: A. Magrelli]

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

The intention to treat the condition with the medicinal product containing genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor was considered justified based on data in a preclinical model showing inhibition of tumour growth.

The condition is life-threatening with a median survival of approximately 12 months.

The condition was estimated to be affecting less than 0.5 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 genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor may be of significant benefit to those affected by the condition. The sponsor has provided data in a preclinical model of the condition showing improved effects when the product is combined with currently available treatments, as well as preliminary clinical data in relapsed patients who responded to treatment. The Committee considered that these observations support a potential for improved efficacy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for genetically modified serotype 5/3 adenovirus coding for granulocyte macrophage colony-stimulating factor, for treatment of malignant mesothelioma, was adopted by consensus.

2.2.30 Product for treatment of pancreatic cancer - EMA/OD/187/14
[COMP Co-ordinator: K. Kubáčková]

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

- Significant benefit

In order to justify the significant benefit of the proposed product the sponsor was invited to discuss the significant benefit in relation to all products authorized for the treatment 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 December meeting.

2.2.31 Product for treatment of primary biliary cirrhosis- EMA/OD/158/13
[COMP Co-ordinator: A. Corrêa Nunes]

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 primary biliary cirrhosis, the sponsor was asked to further elaborate on:

  - the relevance of the preclinical model(s) used for the treatment of primary biliary cirrhosis, 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 its relevance for the development of the product in the condition,
  - the available human clinical data that is directly relevant to the 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 December meeting.

2.2.32 Product for treatment of hypogonadotropic hypogonadism - EMA/OD/126/14
[COMP Co-ordinator: V. Tillmann]

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

- Medical plausibility

The proposed frequency of administration of the product may not be the most appropriate to obtain a stimulation, rather than an inhibition, of gonadotropin secretion. The applicant was asked to provide further justification and discussion of the proposed dosing schedule, in light of the dual effects of GnRH analogues on gonadotropins.

- Number of people affected

The applicant was invited to provide and discuss more data on the relative prevalence of secondary versus primary (idiopathic) HH, and of HH in general. Particularly, the impact of prevalence data from (pan)hypopituitarism on the prevalence on secondary HH.

- Significant benefit

The applicant was asked to provide a more detailed discussion of the assumed significant benefit of the product, particularly in the long-term treatment of HH in adults, versus existing treatments such as sex steroids or injectable gonadotropins.

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 December meeting.

2.2.33 Product for treatment of progressive supranuclear palsy - EMA/OD/141/14
[COMP Co-ordinator: V. Stoyanova]

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 progressive supranuclear palsy, the sponsor was asked to further elaborate on:

  - the mechanism of action in the proposed condition by showing the claimed reduction of neuroinflammation,
  - the relevance of the preclinical model used for the treatment of progressive supranuclear palsy, and the interpretation of the results obtained in the experiments,
  - submit any available data in a specific model of the condition or in preliminary clinical settings in patients affected by the condition.

Without data with the specific product in the specific condition the medical plausibility cannot be accepted.

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 December meeting.

2.2.34 Product for prevention of bronchopulmonary dysplasia - EMA/OD/183/14
[COMP Co-ordinator: B. Bloechl-Daum]

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 prevention of bronchopulmonary dysplasia, the sponsor was asked to further elaborate on:

- any available data with the product as proposed for orphan designation, namely intra-tracheal installation in newborns (e.g. in preclinical models);
- the safety of the product with regards to local administration to premature lungs, in particular in view of the developmental toxicity described for the active substance.

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

2.2.35 Product for treatment of respiratory distress syndrome in neonates- EMA/OD/182/14
[COMP Co-ordinator: M. Možina]

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 respiratory distress syndrome in neonates, the sponsor was asked to further elaborate on:

- any available data with the product as proposed for orphan designation, namely intratracheal installation in newborns (e.g. in preclinical models);
- the safety of the product with regards to local administration to premature lungs, in particular in view of the developmental toxicity described for palifermin.

- Significant benefit

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

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on any available results to justify the assumption of significant benefit over standard of care of 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 December meeting.

2.2.36 Pegylated recombinant human hyaluronidase PH20 for treatment of pancreatic cancer, Pharm. Research Associates (UK) Limited - EMA/OD/173/14
[COMP Co-ordinator: B. Bloechl-Daum]

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

The intention to treat the condition with the medicinal product containing pegylated recombinant human hyaluronidase PH20 was considered justified based on preliminary clinical data showing increased overall response rates in previously untreated patients with stage IV metastatic pancreatic adenocarcinoma, particularly in patients with tumours high in hyaluronan, when the product is administered in addition to standard of care chemotherapy.

The condition is life-threatening in particular due to late diagnosis and poor prognosis in case of unresectable disease and chronically debilitating due to liver insufficiency, cholestasis, cholangitis, weight loss and cachexia.

The condition was estimated to be affecting approximately 1.8 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 pegylated recombinant human hyaluronidase PH20 may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate increased overall response rates, progression-free survival, and overall survival in previously untreated patients with stage IV metastatic pancreatic adenocarcinoma, particularly in patients with tumours high in hyaluronan, when the product is administered in addition to standard of care chemotherapy. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for pegylated recombinant human hyaluronidase PH20, for treatment of pancreatic cancer, was adopted by consensus.

2.2.37 Product for treatment of interstitial cystitis - EMA/OD/179/14
[COMP Co-ordinator: A. Corrêa Nunes]

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

- Number of people affected

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 was asked to re-calculate the prevalence estimate based on relevant European epidemiological studies and registers for the proposed orphan condition.

The COMP adopted a list of issues that will be sent to the sponsor. The sponsor will be invited to answer to the list of issues in writing.

2.2.38 Plerixafor for treatment of WHIM syndrome, Groupe d'étude des neutropénies - EMA/OD/190/14
[COMP Co-ordinator: B. Dembowska-Bagińska]

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

The intention to treat the condition with the medicinal product containing plerixafor was considered justified based on pre-clinical data using a valid model of the condition showing a reversal of circulating pan leukopenia.

The condition is life-threatening due to the risk of developing cancer which is a significant cause of premature mortality and chronically debilitating due to patients suffering from recurrent infections from early childhood as well as numerous warts on hands, feet and trunk.

The condition was estimated to be affecting approximately 0.002 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 plerixafor, for treatment of WHIM syndrome, was adopted by consensus.

2.2.39 Product for treatment of aspartylglucosaminuria - EMA/OD/172/14
[COMP Co-ordinator: I. Bradinova]

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 Aspartylglucosaminuria, the sponsor was asked to further elaborate on:

- the results obtained in in vitro fibroblast cell lines for the treatment of aspartylglucosaminuria;
- the methodology used in the pre-clinical studies as well as the results from these studies and its relevance for the development of the product in the 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 December meeting.

2.2.40 Product for treatment of haemolytic uremic syndrome caused by Shiga toxin-producing bacteria - EMA/OD/194/14
[COMP Co-ordinator: A. Magrelli]

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

- Intention to diagnose, prevent or treat

Haemolytic uremic syndrome caused by Shiga toxin-producing bacteria should be justified as a distinct medical entity or a valid subset, for the purposes of orphan medicinal product designation. The sponsor's attention was drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00). Acknowledging all infectious agents that can cause HUS as well as previous designations the COMP suggests renaming the proposed orphan indication to "treatment of infection-associated haemolytic uremic syndrome".

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of haemolytic uremic syndrome caused by Shiga toxin-producing bacteria, the sponsor was asked to further elaborate on:

- the relevance of the preclinical model used for the treatment of haemolytic uremic syndrome caused by Shiga toxin-producing bacteria, and the interpretation of the results obtained in the experiments,
- any available data with the proposed product in either relevant models of the condition or preliminary clinical data in patients.

In the absence of relevant data with the product in the condition as proposed for designation medical plausibility cannot be assessed.

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

2.2.41 Riluzole for treatment of traumatic spinal cord injury, Dr Laurent Vinay - EMA/OD/186/14
[COMP Co-ordinator: D. Krievins]

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

The intention to treat the condition with the medicinal product containing riluzole was considered justified based on pre-clinical in vivo data in valid models of the condition and preliminary clinical data where improvements in spasticity were noted.

The condition is chronically debilitating due to sensory and motor loss of function in the limbs, and life-threatening due to overall reduced life expectancy.

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 riluzole may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the addition of riluzole improved symptoms associated with spasticity. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for riluzole, for treatment of traumatic spinal cord injury, was adopted by consensus.

2.2.42 Product for treatment for calciphylaxis - EMA/OD/191/14
[COMP Co-ordinator: A. Corrêa Nunes]

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 sodium thiosulphate for the treatment of calciphylaxis, the sponsor was invited to further elaborate on:

- the availability of non-clinical studies which are validated as models for the condition to establish proof of principle that sodium thiosulphate is effective in calciphylaxis;

- the availability of case reports in calciphylaxis patients successfully treated with sodium thiosulphate.

In the absence of relevant data of this product in the disease applied for orphan designation medical plausibility cannot be established.

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 December meeting.

2.2.43 Product for treatment of Aicardi-Goutières syndrome - EMA/OD/205/14
[COMP Co-ordinator: A. Corrêa Nunes]

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 Aicardi-Goutières syndrome, the sponsor was asked to further elaborate on:

- how the in vivo model supports the medical plausibility in all AGS types;
- what the difference is in the pathogenic mechanism between AGS types 1-5 and AGS6-7, and why the latter could not be included in the OD;
- how the treatment can practically be given in the time window required to halt the neurological damage;
- whether there is a risk that the proposed treatment strategy (treatment only in the initial stages of the disease) does not abrogate but simply postpone the neurological disease process to a later time point/older age;
- whether the product crosses the blood–brain barrier (if this is indeed required).

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 December meeting.

2.2.44 Product for treatment of Pseudomonas Aeruginosa infections in cystic fibrosis patients- EMA/OD/174/14
[COMP Co-ordinator: J. Eggenhofer]

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

- Medical plausibility

In order to justify the medical plausibility of the proposed product the sponsor was invited to elaborate on the grounds for assuming equal efficacy of the proposed product *vis a vis* currently authorized formulations for inhalation of the product, taking into account the lack of in vivo data with the proposed formulation at the present stage.

- Significant benefit

In order to justify the significant benefit of the proposed product the sponsor was invited to elaborate on:

- any available data supporting an assumption of potential better tolerability than the currently authorized formulations of the product;

- any available data supporting the claims of major contribution to patient care with the proposed formulation, and any available data documenting difficulties and problems with the currently authorised products.

In absence of any data the significant benefit cannot be acknowledged.

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 December meeting.

2.2.45 Product for treatment of Wilson's disease - EMA/OD/201/14
[COMP Co-ordinator: K. Westermark]

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

- Significant benefit

The sponsor was invited to provide evidence of lack of supply of the authorised trientine to EU member states and a survey of the availability of trientine dihydrochloride, including all member states should be performed to provide data on the real availability/access to trientine dihydrochloride in the EU.

The sponsor was invited to provide any available clinical data from the French patient material or other sources to support the claims of improved safety, convenience (especially with regard to paediatric use) and compliance.

The sponsor was invited to provide comparative and supportive stability data comparing the product and the authorised counterpart.

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 December meeting.

2.3. Appeal procedure

None.

2.4. Evaluation on-going

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

2.5. Validation on-going

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

3. Requests for protocol assistance

3.1 For treatment of hepatocellular carcinoma [COMP Coordinator: A. Magrelli]

The Committee was briefed on the significant benefit issues. The COMP answer on the significant benefit issues was adopted.

3.2 For treatment of functional gastro-entero-pancreatic endocrine tumours [COMP Coordinator: B. Bloechl-Daum]

The Committee was briefed on the significant benefit issues. The COMP answer on the significant benefit issues was adopted.

3.3 For treatment of acute myeloid leukaemia [COMP Coordinator: K. Westermark]

The Committee was briefed on the significant benefit issues. The COMP answer on the significant benefit issues was adopted.

4. Overview of applications

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

COMP co-ordinators were appointed for 3 applications submitted and 37 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 Cyramza (ramucirumab) for treatment of gastric cancer; Eli Lilly Nederland B.V. (EU/3/12/1004) [COMP Co-ordinator: B. Bloechl-Daum]

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

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

- Proposed indication

The sponsor was invited to justify whether adenocarcinoma of the gastroeosophageal junction falls within the distinct medical entity as designated. The sponsor was asked to compare and contrast gastric cancer and cancer of the gastroesophageal junction in terms of classification, pathogenesis, etiology and clinical characteristics.

- Prevalence

The sponsor was requested to provide an updated prevalence calculation for gastric cancer at the time of the review of criteria for designation.

- Justification of significant benefit

In the maintenance document provided at this point in time, the sponsor provided a general discussion without any data and asserts that that the product as a single agent constitutes a clinically relevant advantage due to a different and more tolerable safety profile than other agents used.

Instead, the sponsor was hereby requested to provide data from the available clinical studies (monotherapy or in combination with paclitaxel) to document a clinically relevant advantage (such as improved efficacy or improved safety) or major contribution to patient care, in the context of the current standard of care guidelines for the gastric cancer population for which marketing authorisation is sought.

In particular with regards to the RAINBOW study: the sponsor was asked to discuss the clinical relevance of the extent of the OS improvement, as well as the results in the secondary endpoints studied, for the purpose of justifying significant benefit.

In its written response, and during an oral explanation before the Committee on 11 November 2014, the sponsor further elaborated on the issues raised. With regards to the indication and the inclusion of

GEJ cancers, the sponsor referred to ICD-10 codes and the commonalities in classification and treatment. The sponsor compared and contrasted EC, GEJC ad GC. The COMP considered that the GEJC is encompassed by the designation indication.

As per the prevalence issue, the sponsor discussed that the conclusion of 2.88 up to 4.24, based on both direct and indirect methods of estimate calculation, would include the GEJ. The COMP considered based on this data that the prevalence criterion is still met.

Finally with regards to the justification of significant benefit, the sponsor referred to gastric cancer treatment guidelines for second line therapy, and discussed single agent treatment with irinotecan, docexatel, or paclitaxel, or rechallenged by the previous chemotherapeutic regimen.

The sponsor noted that in the context of the very short survival in patients with advanced gastric cancer, the improvement of the rainbow study +2.3 m versus BSC is significant.

The COMP discussed the relevance of the patient population who had metastatic or non-resectable, locally advanced or gastro-oesophageal junction adenocarcinoma with disease progression during or within 4 months after the last dose of first-line therapy. It was considered that the additional 2.3 months seen in the combination with paclitaxel was considered to be a clinically relevant advantage as these patients have a short survival expectation.

In the case of monotherapy the improvement of 1.4 months and the tolerance observed with ramucirumab was considered to be of a clinically relevant advantage in patients who had advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum or fluoropyrimidine chemotherapy, for whom treatment in combination with paclitaxel is not appropriate.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated orphan medicinal product.

The prevalence of gastric cancer (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be not more than 4 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening with poor overall 5 year survival: less than 5 to 15% because most patients present with advanced disease.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Cyramza used in combination may be of potential significant benefit has been demonstrated as an additional survival of 2 months in patients with gastric cancer who were refractory or had unresectable cancer and was considered relevant. In the case of the monotherapy the improved tolerability was considered of significant benefit in these patients as well.

An opinion not recommending the removal Cyramza, ramucirumab, (EU/3/12/1004) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

5.1.2 Lynparza (olaparib) for treatment of ovarian cancer; AstraZeneca AB (EU/3/07/501) [COMP Co-ordinator: B. Bloechl-Daum]

The COMP noted the CHMP opinion on MA adopted 20-23 October 2014 meeting.

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

- Proposed indication

The sponsor was asked to compare and contrast ovarian cancer, fallopian tube and primary peritoneal cancer with regards to aetiology, classification, pathophysiology and clinical characteristics, to justify the inclusion of fallopian and peritoneal patient populations in the orphan designated indication.

- Significant benefit

The sponsor was invited to further elaborate on the significant benefit and justify based on data a clinically relevant advantage or major contribution to patient care versus all authorised counterparts, for the population the marketing authorisation is sought.

In its written response, and during an oral explanation before the Committee on 11 November 2014, the sponsor defended the inclusion of fallopian and primary peritoneal cancer, by mainly three arguments: common tissue origin, common molecular pathology, and common clinical characteristics and natural history leading to the same staging and treatment. The COMP agreed that the same aetiology and clinical characteristics can allow for the inclusion of these three tumours into the orphan designated condition.

As for the significant benefit argument the sponsor stressed that the product has been authorised for maintenance therapy in forms of the disease carrying a mutation of the BRCA gene. The sponsor pointed out that "the only other available maintenance therapy bevacizumab is not targeted to any particular subgroup of patients and is commenced together with chemotherapy and continued as a maintenance therapy until disease progression delivering a median PFS improvement of 4 months longer than chemotherapy alone. There is no comparable data for bevacizumab when initiated after completion of chemotherapy in PSR patients. The treatment benefit of olaparib maintenance after completion of chemotherapy, prolonging median PFS by 6.9 months longer than placebo in BRCA mutated patients, compares favourably with all other available treatment options".

The sponsor informed the COMP that there was no data with their product comparing bevacizumab in the context of patients with BRCA mutated (germline and/or somatic) high grade serous epithelial ovarian, fallopian tube, and primary peritoneal cancer. The COMP deliberated on the importance of having comparative data in order to establish a clinically relevant advantage. Members recognised the importance of having this data in order to be able to establish the clinically relevant advantage, however it was also noted that in the current ESMO guidelines on non-epithelial ovarian cancer (Annals of Oncology 23 (Supplement 7):vii20-vii26, 2012) the place of this therapy is not clear. The benefit of using bevacizumab in advanced stages and recurrences is noted to be "of potential interest". It was also noted that the current guidelines do not clearly establish what an acceptable treatment algorithm would be for the BRCA mutated patients.

The current bevacizumab SPC Section 4.1 does not specify its use in BRCA mutated patients although it does specify how it should be used in ovarian cancer patients (front-line therapy in combination with carboplatin and paclitaxel, in combination with carboplatin and gemcitabine, is indicated for treatment of adult patients with first recurrence of platinum-sensitive ovarian cancer and combination with paclitaxel, topotecan, or pegylated liposomal doxorubicin is indicated for the treatment of adult patients with platinum-resistant recurrent ovarian cancer).

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of ovarian cancer (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be approximately 3 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is chronically debilitating in particular due to pain, weight loss, ascites and vaginal bleeding, and life-threatening with approximately half of the patients surviving less than five years.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Lynparza (olaparib) may be of potential significant benefit to those affected by the orphan condition has been justified on the grounds of targeting maintenance treatment of BRCA mutated tumours in patients who have responded to platinum based chemotherapy.

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated orphan medicinal product orphan indication.

An opinion not recommending the removal of Lynparza, olaparib (EU/3/07/501) from the EC Register of Orphan Medicinal Products was adopted by consensus.

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

5.1.3 Scenesse ([Nle4, D-Phe7]-alfa-melanocyte stimulating hormone) for treatment of erythropoietic protoporphyria; Clinuvel (UK) Limited
(EU/3/08/541) [COMP Co-ordinator: L. Gramstad]

The COMP noted the CHMP opinion on MA adopted 20-23 October 2014 meeting.

The COMP concluded that:

The proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product.

The prevalence of erythropoietic protoporphyria (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded to be less than 0.2 in 10,000 persons in the European Union, at the time of the review of the designation criteria.

The condition is life-threatening as patients may die from liver failure and is chronically debilitating due to skin photosensitivity, anaemia and liver complications.

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 of Scenesse, [Nle4, D-Phe7]-alfa-melanocyte stimulating hormone, afamelanotide, (EU/OD/108/07) from the EC Register of Orphan Medicinal Products was 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 (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) [COMP Co-ordinator: A. Correa Nunes]

For information.

5.2.2 Nintedanib for treatment of idiopathic pulmonary fibrosis; Boehringer Ingelheim International GmbH (EU/3/13/1123) [COMP Co-ordinator: A. Moraiti]

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 December meeting.

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

5.3.3 Cysteamine hydrochloride for treatment of cystinosis; Orphan Europe S.A.R.L. (EU/3/08/578)

5.3.4 Panobinostat for treatment of multiple myeloma; Novartis Europharm Limited (EU/3/12/1063)

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 Tasimelteon for treatment of non-24-hour sleep-wake disorder in blind people with no light perception; Vanda Pharmaceuticals Limited (EU/3/10/84)

5.3.7 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)

5.3.8 Ruxolitinib for treatment of polycythaemia vera; Novartis Europharm Limited (EU/3/14/1244)

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

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

5.3.11 Lenvatinib; Eisai Ltd

a) treatment of papillary thyroid cancer (EU/3/13/1121)

b) treatment of follicular thyroid cancer (EU/3/13/1119)

5.3.12 Susoctocog alfa for treatment of haemophilia A; Baxter AG (EU/3/10/784)

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

5.3.14 Glyceryl tri-(4-phenylbutyrate); Hyperion Therapeutics Limited:

a) treatment of carbamoyl-phosphate synthase-1 deficiency (EU/3/10/733)

b) treatment of ornithine carbamoyltransferase deficiency (EU/3/10/734)

c) treatment of citrullinaemia type 1 (EU/3/10/735)

d) treatment of argininosuccinic aciduria (EU/3/10/736)

e) treatment of hyperargininaemia (EU/3/10/737)

f) treatment of ornithine translocase deficiency (hyperornithinaemia-hyperammonaemia homocitrullinuria (HHH) syndrome) (EU/3/10/738)

g) treatment of citrullinaemia type 2 (EU/3/10/739)

5.3.15 Idebenone for treatment of Leber's hereditary optic neuropathy; Santhera Pharmaceuticals (Deutschland) GmbH (EU/3/07/434)

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

5.3.17 Asfotase alfa for treatment of hypophosphatasia; Alexion Europe SAS (EU/3/08/594)

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

5.3.19 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride for treatment of narcolepsy; Bioprojet (EU/3/07/459)

5.3.20 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 Draft Work plan for the European Medicines Agency Human Scientific Committees' Working Party with Healthcare Professionals' Organisations (HCPWP) 2015 (EMA/515424/2014)

EMA presented the topic.

6.2 Draft Work plan for the European Medicines Agency Human Scientific Committees' Working Party with Patients' and Consumers' Organisations (PCWP) 2015 (EMA/463774/2014)

EMA presented the topic.

7. Any other business

7.1 2014 report on the State of the Art of Rare Disease activities in Europe by European Union Committee of Experts on Rare Diseases (EUCERD)

The report was circulated for information.

7.2 Presentations from the joint CHMP/CAT/COMP meeting held on 28-30 October 2014 in Rome

Presentations were circulated for information.

Date of next COMP meeting: 9-11 December 2014

Annex to the Minutes of the COMP of November 2014

List of Participants and Documentation on Declaration of interest of members and experts

Based on the Declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of Committee members for the upcoming discussions.

In accordance with the Agency's revised Policy and Procedure on the handling of conflicts of interests, participants in this meeting were asked to declare any conflict of interests on the matters for discussion (in particular any changes, omissions or errors to the already declared interests).

No new or additional conflicts were declared.

COMP Chair	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restrictions applies Product / substance
Bruno Sepodes		Full involvement	

COMP Member	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restrictions applies Product / substance
Brigitte Blöchl-Daum	Austria	Full involvement	
André Lhoir	Belgium	Full involvement	
Irena Bradinova	Bulgaria	Full involvement	
Kateřina Kubáčková	Czech Republic	DP	3.1.
Jens Ersbøll	Denmark	Full involvement	
Vallo Tillmann	Estonia	Full involvement	
Karri Penttila	Finland	Full involvement	
Annie Lorence	France	Full involvement	
Nikolaos Sypsas	Greece	Full involvement	
Judit Eggenhofer	Hungary	Full involvement	
Sigurdur B. Thorsteinsson	Iceland	Full involvement	

COMP Member	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restrictions applies Product / substance
Geraldine O'Dea	Ireland	Full involvement	
Armando Magrelli	Italy	Full involvement	
Dainis Krievins	Latvia	Full involvement	
Aušra Matulevičienė	Lithuania	Full involvement	
Albert Vincenti	Malta	Full involvement	
Lars Gramstad	Norway	Full involvement	
Bożenna Dembowska-Bagińska	Poland	Full involvement	
Ana Corrêa-Nunes	Portugal	Full involvement	
Flavia Saleh	Romania	Full involvement	
Zuzana Batová	Slovak Republic	Full involvement	
Martin Možina	Slovenia	Full involvement	
Josep Torrent Farnell	Spain	Full involvement	
Kerstin Westermark	Sweden	Full involvement	
Violeta Stoyanova-Beninska	The Netherlands	Full involvement	
Daniel O'Connor	United Kingdom	Full involvement	

COMP Member nominated by the European Commission on the EMA's recommendation	Role	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product / substance
Ingeborg Barisic	Member		Full involvement	
Giuseppe Capovilla	Member		Full involvement	
Aikaterini Moraiti	Member		Full involvement	

Patients' organisations representatives nominated by the European Commission	Role	Country	Outcome restriction following evaluation of e-DoI for the meeting	Topics on the current Committee Agenda for which restriction applies Product / substance

Patients' organisations representatives nominated by the European Commission	**Role**	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting**	**Topics on the current Committee Agenda for which restriction applies** **Product/ substance**
Lesley Greene	COMP vice-chair	Eurordis	Full involvement	
Birthe Byskov Holm	Member	Eurordis	Full involvement	
Marie Pauline J. Evers	Member	EGAN	Full involvement	

EUROPEAN COMISSION	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting**	**Topics on the current Committee Agenda for which restrictions applies** **Product/substance**
	European Commission	Full involvement	

COMP Experts/ Observers	**Country**	**Outcome restriction following evaluation of e-DoI for the meeting**	**Topics on the current Committee Agenda for which restrictions applies** **Product/substance**
Virginie Hivert	Eurordis		
Michel Hoffmann	Luxembourg		
Jana Schweigertova	Slovak Republic		

Discussions, deliberations and voting took place in full respect of the restricted involvement of Scientific Committee members and, where relevant, experts attending the plenary meeting, as announced by the Scientific Committee Secretariat at the start of meeting.

Restriction levels:

Evaluation of the conflict of interest	
Outcome	Impact
R-P	To be replaced for the discussions, final deliberations and voting as appropriate in relation to the relevant product or a competitor product.

XP	Where Individual product involvement is declared - PRODUCT INDICATION: - No involvement with respect to procedures involving the relevant product or a competitor product in the relevant indication i.e. no part in discussions, final deliberations and voting as appropriate as regards these medicinal products. - Cannot act as Rapporteur for these products - [Cannot act as Rapporteur for development of guidelines in concerned therapeutic area].
XC	Where cross product / general involvement is declared - COMPANY: - No involvement (as outlined above) with respect to products from the specified company. - Cannot act as Rapporteur for products from the relevant company(ies).
DP	Where Individual product involvement is declared - PRODUCT INDICATION: - Involvement in discussions only with respect to procedures involving the relevant product or a competitor product i.e. no part in final deliberations and voting as appropriate as regards these medicinal products. - Cannot act as Rapporteur for these products.
DC	Where cross product / general involvement is declared - COMPANY: - Involvement in discussions only with respect to products from the specified company. - Cannot act as Rapporteur on products from the relevant company(ies).
XR	Committee member cannot act as Rapporteur or Peer reviewer in relation to any medicinal product from the relevant company.
R-C	To be replaced for the discussions, final deliberations and voting as appropriate in relation to any medicinal product from the relevant company