3 November 2014
EMA/COMP/427307/2014 Rev. 1
Procedure Management and Business Support Division

Committee for Orphan Medicinal Products (COMP)

Minutes of the 2-4 September 2014 meeting

Note on access to documents

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

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1. Introduction

1.1 Adoption of the agenda, EMA/COMP/432344/2014

The agenda was adopted with no amendments.

1.2 Adoption of the minutes of the previous meeting, 8-10 July 2014 EMA/COMP/357442/2014

The minutes were adopted with minor corrections to points 2.1.8 and 2.1.9.

1.3 Conflicts of Interest

The Chair asked the Committee members to declare conflicts of interest that have not been identified prior to the meeting.

The COMP secretariat was informed of the following:

- EGAN received a grant from the sponsors of the product under agenda point 5.1.1. Nevertheless, no direct conflicts of interest have been identified for P. Evers (EGAN), Patient Representative in the COMP.

2. Applications for orphan medicinal product designation[1]

2.1. For opinion

2.1.1 Product for treatment of neuromyelitis optica - EMA/OD/089/14
[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 neuromyelitis optica, the sponsor should further elaborate on:

  - the absence of any data with the product in neuromyelitis optica as applied for designation;
  - the unpublished case report with regards to previous treatments and assessments;
  - the improvements argued in this patient vis a vis the natural course of the condition.

In the written response, and during an oral explanation before the Committee on 2 September 2014, the sponsor further elaborated on the proposed mechanism of action, focusing on reduced survival and function of T-cells and Antigen Presenting Cells. The sponsor also further elaborated on the case of a patient treated with the product; it was argued that following administration, a period without relapse or deterioration was observed.

The COMP considered that it would be difficult to consider the medical plausibility in the absence of proof of concept studies and the uncontrolled and unclear nature of the observations presented in the

[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).

discussed case report. In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 2 September 2014, prior to final opinion.

2.1.2 Product for treatment of systemic-onset juvenile idiopathic arthritis - EMA/OD/108/14
[COMP Co-ordinator: A. Corrêa Nunes]

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 systemic-onset juvenile idiopathic arthritis, the sponsor should further elaborate on:

  - the mechanism of action of the product;
  - the relevance of the preclinical model used for the treatment of systemic-onset juvenile idiopathic arthritis, and the interpretation of the results obtained in the experiments;
  - any further available data in either relevant models or preliminary clinical settings, in patients affected by the condition.

- Significant benefit

The sponsor was requested to further discuss the arguments provided for significant benefit and to elaborate on the results from any 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 2 September 2014, the sponsor elaborated on the proposed mechanism of action, focusing on in vivo inhibition of pro-inflammatory cytokines. The sponsor also discussed that the model used for the purpose of medical plausibility shares certain features with the proposed condition, such as inflammation of the joints and expression of pro-inflammatory cytokines, and also referred to clinical studies in healthy volunteers. With regards to the significant benefit, the sponsor argued that the product acts via a new mechanism of action that might help patients who don't currently respond to current biologic treatments.

The COMP considered that in the absence of proof of concept data, it would be difficult to draw conclusions for the medical plausibility and significant benefit issues.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 3 September 2014, prior to final opinion.

2.1.3 (S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-5-carbonitrile for treatment of Pemphigus, Almirall S.A. - EMA/OD/091/14
[COMP Co-ordinator: B. Bloechl-Daum]

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 Pemphigus, the sponsor should further elaborate on:

- the fact that several preclinical models for Pemphigus have been described in the literature and are absent in the present application.

- 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 should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition, using the most conservative incidence figures and taking into consideration the lifelong duration of 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 requested to further discuss the arguments provided for significant benefit and to elaborate on how the results in the chosen animal model justify the assumption of significant benefit in the proposed condition. The sponsor was further requested to justify the assumption of significant benefit over all authorised medicinal products for the proposed orphan indication.

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

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

In the written response, and during an oral explanation before the Committee on 2 September 2014, the sponsor justifies the use of the preclinical models in the application and presented additional data in another preclinical model of the condition, in which the product had an effect on the skin lesions. The sponsor also presented a revised prevalence calculation based on the most conservative incidence estimates reported in the literature. The COMP considered this revised prevalence estimate acceptable.

With regards to significant benefit, the sponsor proposed that based on its mode of action the product may be a disease modifier, which could be used as an alternative or in combination with current treatments . This argument is supported by preclinical results, demonstrating additive effects when the product is administered concomitantly with prednisolone.

In conclusion, the COMP considered that the sponsor has provided data from preclinical models that demonstrate favourable effect on skin lesions and auto-antibody titres. The Committee considered that this may translate into a clinically relevant advantage for patients affected by the condition if supported by data at the time of marketing authorisation.

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

The intention to treat the condition with the medicinal product containing (S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-5-carbonitrile was considered justified based on preclinical data in relevant models of the disease.

The condition is chronically debilitating and potentially life threatening due to chronic blistering associated with dehydration and secondary infection which can lead to premature death.

The condition was estimated to be affecting approximately 3.27 per 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 (S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-5-carbonitrile may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data showing a favourable effect on skin lesions and auto-antibody titres. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for (S)-2-(1-((6-amino-5-cyanopyrimidin-4-yl)amino)ethyl)-4-oxo-3-phenyl-3,4-dihydropyrrolo[2,1-f][1,2,4]triazine-5-carbonitrile, for treatment of pemphigus, was adopted by consensus.

2.1.4 (*S*)-6-hydroxy-2,5,7,8-tetramethyl-*N*-((*R*)-piperidin-3-yl)chroman-2-carboxamide hydrochloride for treatment of Leigh syndrome, Khondrion BV - EMA/OD/068/14

[Co-ordinators: A. Magrelli] [Expert: S. Rahman]

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 should further elaborate on:

  - the results of the rotarod measurements seemingly showing faster time to fall in treated versus untreated subjects in the wild-type group. The sponsor is also invited to elaborate on the clinical relevance of the increase in time to fall in the used model;
  - the relevance of the preclinical chosen mouse model to the proposed 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".

The sponsor should justify the proposed prevalence estimate of the condition, identifying and critically assessing sources and the methodology used for the prevalence calculation.

In the written responses and during the oral explanation the sponsor further clarified the relevance of the preclinical model to the pathogenesis and clinical phenotype of Leigh syndrome. It was discussed that in this model subjects have a neurodegenerative phenotype characterized by neuronal deterioration and gliosis with primary involvement of the vestibular nuclei, cerebellum, and olfactory bulb, sufficiently resembling the pathogenesis of the human condition. The relevance of the rotarod measurements was also further elaborated, and the sponsor also reported about additional experiments performed at different time points. An updated prevalence calculation was also presented.

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

The intention to treat the condition with the medicinal product containing (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride was considered justified based on preclinical data in relevant models of the disease.

The condition is chronically debilitating due to neurological deficits, psychomotor delay, dysmorphic features, cardiac, renal and endocrine dysfunction, and life-threatening with most patients dying in early childhood.

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

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

A positive opinion for (S)-6-hydroxy-2,5,7,8-tetramethyl-N-((R)-piperidin-3-yl)chroman-2-carboxamide hydrochloride (KH-176), for treatment of Leigh syndrome, was adopted by consensus.

2.1.5 Immunoglobulin G1, anti-(human tumour-associated calcium signal transducer 2)(human-Mus musculus monoclonal hRS7 heavy chain), disulfide with human-Mus musculus monoclonal hRS7 κ-chain, dimer, hexakis(thioether) with (4S)-4-[[[[4-[[(2S)-2-(4-aminobutyl)-2-[[2-[2-[[26-[4-[[[[4-[(3-mercapto-2,5-dioxo-1-pyrrolidinyl)methyl]cyclohexyl]carbonyl]amino]methyl]-1H-1,2,3-triazol-1-yl]-3,6,9,12,15,18,21,24-octaoxahexacos-1-yl]amino]-2-oxoethoxy]acetyl]amino]-1-oxoethyl]amino]phenyl]methoxy]carbonyl]oxy]-4,11-diethyl-9-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione for treatment of pancreatic cancer, Immunomedics GmbH – EMA/OD/081/14

[COMP Co-ordinator: B. Bloechl-Daum]

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 should further elaborate on:

  - the preliminary results from the on-going Phase I/II study in patients with relapsed/refractory pancreatic cancer.

- Significant benefit

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

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

The sponsor should detail the results of any clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

In the written response, and during an oral explanation before the Committee on 2 September 2014, the sponsor presented more in detail information on the preliminary clinical trial data used in this submission. A key finding result discussed was the time to progression (TTP) for 15 patients who were relapsed or refractory to previous treatments. Standard therapy had been used first line in the treatment of pancreatic cancer (the regimes were shown for each patient). The TTP was shown to be

prolonged in those patients who received the sponsor's product. This data was considered sufficient to support the basis of medical plausibility and significant benefit.

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 immunoglobulin G1, anti-(human tumour-associated calcium signal transducer 2)(human-Mus musculus monoclonal hRS7 heavy chain), disulfide with human-Mus musculus monoclonal hRS7 κ-chain, dimer, hexakis(thioether) with (4S)-4-[[[[4-[[(2S)-2-(4-aminobutyl)-2-[[2-[2-[[26-[4-[[[[4-[(3-mercapto-2,5-dioxo-1-pyrrolidinyl)methyl]cyclohexyl]carbonyl]amino]methyl]-1H-1,2,3-triazol-1-yl]-3,6,9,12,15,18,21,24-octaoxahexacos-1-yl]amino]-2-oxoethoxy]acetyl]amino]-1-oxoethyl]amino]phenyl]methoxy]carbonyl]oxy]-4,11-diethyl-9-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione was considered justified based on preliminary clinical data in patients with the condition.

The condition is chronically debilitating because of pain in the upper abdomen, loss of appetite, nausea, vomiting, weight loss, jaundice, fatigue, weakness and depression, and life-threatening with a median survival of about 6 months.

The condition was estimated to be affecting approximately 0.4 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 immunoglobulin G1, anti-(human tumour-associated calcium signal transducer 2)(human-Mus musculus monoclonal hRS7 heavy chain), disulfide with human-Mus musculus monoclonal hRS7 κ-chain, dimer, hexakis(thioether) with (4S)-4-[[[[4-[[(2S)-2-(4-aminobutyl)-2-[[2-[2-[[26-[4-[[[[4-[(3-mercapto-2,5-dioxo-1-pyrrolidinyl)methyl]cyclohexyl]carbonyl]amino]methyl]-1H-1,2,3-triazol-1-yl]-3,6,9,12,15,18,21,24-octaoxahexacos-1-yl]amino]-2-oxoethoxy]acetyl]amino]-1-oxoethyl]amino]phenyl]methoxy]carbonyl]oxy]-4,11-diethyl-9-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that there is an effect on the time to progression in patients with relapsed or refractory pancreatic cancer who were treated with the product. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for immunoglobulin G1, anti-(human tumour-associated calcium signal transducer 2)(human-Mus musculus monoclonal hRS7 heavy chain), disulfide with human-Mus musculus monoclonal hRS7 κ-chain, dimer, hexakis(thioether) with (4S)-4-[[[[4-[[(2S)-2-(4-aminobutyl)-2-[[2-[2-[[26-[4-[[[[4-[(3-mercapto-2,5-dioxo-1-pyrrolidinyl)methyl]cyclohexyl]carbonyl]amino]methyl]-1H-1,2,3-triazol-1-yl]-3,6,9,12,15,18,21,24-octaoxahexacos-1-yl]amino]-2-oxoethoxy]acetyl]amino]-1-oxoethyl]amino]phenyl]methoxy]carbonyl]oxy]-4,11-diethyl-9-hydroxy-1H-pyrano[3',4':6,7]indolizino[1,2-b]quinoline-3,14(4H,12H)-dione for treatment of pancreatic cancer, was adopted by consensus.

2.1.6 Cannabidiol for treatment of Dravet syndrome, GW Pharma Ltd - EMA/OD/083/14
[COMP Co-ordinator: I. Bradinova]

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 Dravet syndrome, the sponsor should further elaborate on:

  - the methodology used in the preclinical studies as well as the results from these studies and discuss their relevance for the development of the product in the condition as applied for designation;
  - the methodology used in the preliminary clinical studies and specifically discuss the Dravet syndrome patients with regards to the treatments received before and during the study and the assessments performed. Any further available preliminary clinical data in Dravet patients should be presented to the COMP.

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

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor is invited to substantiate these claims with any data that may be available. A significant benefit justification versus all authorised products, including stiripentol, should be further elaborated.

In the written response, and during an oral explanation before the Committee on 2 September 2014, the sponsor presented new data and in particular discussed observations from 13 children with Dravet syndrome who were treated with the proposed product. Patients were resistant to antiepileptics and continued their various concomitant medications during the observation period. The sponsor reported that approximatley a third of the patients had significant seizure reduction. A revised prevalence calculation was also presented.

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

The intention to treat the condition with the medicinal product containing cannabidiol was considered justified based on preliminary clinical data in patients with the condition.

The condition is chronically debilitating due to psychomotor and cognitive impairment and the occurrence of convulsive seizures, and life-threatening in particular due to generalized tonic-clonic seizures.

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 cannabidiol may be of significant benefit to those affected by the condition. The

sponsor has provided clinical data that demonstrate that when used in combination with anticonvulsants there was a clinically relevant reduction in seizures associated with the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for cannabidiol, for treatment of Dravet syndrome, was adopted by consensus.

2.1.7 Cultured allogeneic corneal limbal stem cells for treatment of limbal stem cell deficiency, NHS National Services Scotland Trading as Scottish National Blood Transfusion Service - EMA/OD/109/14
[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 limbal stem cell deficiency, the sponsor should further elaborate on:

  - the results from the on-going clinical study performed by the sponsor are unclear. The sponsor was invited to provide further available data on the preliminary results in those patients treated, highlighting the parameters relevant to the condition.

- Number of people affected

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

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 the written response, and during an oral explanation before the Committee on 3 September 2014, the sponsor further elaborated on the preliminary results of the clinical safety study they are currently conducting where they measured some secondary efficacy parameters and compared their active product to a control group. Of interest for the COMP were the preliminary results seen in the active treated group where an improvement in most measures of the corneal surface for the majority of the patients was seen (approximately 50% improved from severe/moderate to mild/no effect scoring). Visual acuity improvement was seen in 4 out of 8 patients as compared to 2 out of 7 patients and functional impairment score improved in 3 out of 6 patients as compared with 1 out of 4 patients. Based on these results the COMP considered this was sufficient to support the medical plausibility. The revised prevalence calculation was also considered acceptable.

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

The intention to treat the condition with the medicinal product containing cultured allogeneic corneal limbal stem cells was considered justified based on preliminary clinical data in patients with the condition.

The condition is chronically debilitating due to discomfort of a thickened, irregular and unstable corneal surface and reduced or complete loss of vision.

The condition was estimated to be affecting approximately 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 cultured allogeneic corneal limbal stem cells, for treatment of limbal stem cell deficiency, was adopted by consensus.

2.1.8 **Osilodrostat** for treatment of Cushing's syndrome, Novartis Europharm Limited - EMA/OD/099/14

[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 treatment of Cushing's syndrome, the sponsor should further elaborate on any available data in patients with Cushing's syndrome apart from Cushing's disease (ACTH-secreting pituitary adenoma).

- Significant benefit

The sponsor is requested to further discuss the arguments provided for significant benefit based on available data to justify the assumption of significant benefit over all authorised medicinal products for the proposed orphan indication.

In the written response, and during an oral explanation before the Committee on 3 September 2014, the sponsor stated that currently no data are available in patients with Cushing's syndrome apart from Cushing's disease. The sponsor however justifies that due to the product's mode of action, targeting the final step of cortisol synthesis, it was highly plausible that the product would be effective in all forms of Cushing's disease. The sponsor further elaborates on the high response rate in the Phase II study presented in the application, which according to the sponsor is higher than with any other currently approved compound.

With regards to significant benefit the sponsor discusses the efficacy of the product over authorised products based on historical data. The sponsor emphasizes that preliminary clinical data of the proposed product support the assumption of significant benefit over authorised treatments.

In conclusion, the COMP considered that the sponsor has provided preliminary clinical data demonstrating significant effects on 24 hour free urinary cortisol levels in patients with Cushing's disease. The Committee considered that this may translate into a clinically relevant advantage for patients affected by the condition, if supported by data at the time of marketing authorisation

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

The intention to treat the condition with the medicinal product containing osilodrostat was considered justified based on preliminary clinical data in patients with Cushing's disease.

The condition is life-threatening and chronically debilitating due to the consequences of hypercortisolism, including cardiovascular disease, diabetes, clotting disorders, muscular weakness and osteoporosis, and psychiatric conditions.

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

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 osilodrostat may be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data demonstrating significant effects on 24 hour free urinary cortisol levels in patients with Cushing's disease. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for 4-[(5R)-6,7-Dihydro-5H-pyrrolo[1,2-c]imidazol-5-yl]-3-fluorobenzonitrile phosphate, for treatment of Cushing's syndrome, was adopted by consensus.

2.1.9 ***Oxalobacter formigenes*** **strain HC-1** for treatment of short bowel syndrome, OxThera AB - EMA/OD/080/14

[COMP Co-ordinator: D. Krievins]

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 short bowel syndrome, the sponsor should further elaborate on:

  - the relevance of the preclinical model used for the treatment of short bowel syndrome, and the interpretation of the results obtained in the experiments, in particular with regards to how the disturbed intestinal environment associated with short-bowel syndrome would affect the product;

- 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 data of the product in the proposed condition and results from 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 3 September 2014, the sponsor further justified the relevance of the preclinical models used for the treatment of the condition. In support of both, medical plausibility and significant benefit, the sponsor presented preliminary clinical data showing a decrease in plasma- and urine oxalate levels upon treatment with the product.

In conclusion, the COMP considered that the sponsor has provided data from preclinical models and preliminary clinical data from a patient affected by the condition that suggest favourable effects on secondary hyperoxaluria in short-bowel syndrome. The Committee considered that this may translate into a clinically relevant advantage for patients affected by the condition, if supported by data at the time of marketing authorisation.

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

The intention to treat the condition with the medicinal product containing *Oxalobacter formigenes* strain HC-1 was considered justified based on preclinical and preliminary clinical data in the condition demonstrating favourable effects on plasma- and urine oxalate levels.

The condition is chronically debilitating due to severe nutritional deficiency, metabolic and/or septic complications and life-threatening liver failure and end stage renal disease.

The condition was estimated to be affecting not more than 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 *Oxalobacter formigenes* strain HC-1 may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate efficacy in preclinical models of hyperoxaluria and preliminary clinical data showing a decrease in plasma- and urine oxalate levels. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for *Oxalobacter formigenes* strain HC-1, for treatment of short bowel syndrome, was adopted by consensus.

2.1.10 Product for treatment of cytomegalovirus (CMV) infections in patients following allogeneic stem cell transplantations - EMA/OD/096/14
[COMP Co-ordinator: B. Dembowska-Bagińska]

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

Cytomegalovirus infections following allogeneic stem cell transplantation should be justified as a distinct medical entity or a valid subset. Note that this is 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). The sponsor was invited to further justify sub-setting the broader condition of impaired cell-mediated immunity and restricting the use of the product only to patients who received HSCT.

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of cytomegalovirus infections following allogeneic stem cell transplantation, the sponsor should further elaborate on:

- the timing of administration of the proposed product, with particular attention to whether the use would be preventive or for treatment;
- the feasibility of the intended clinical use of the product, linked to the need of the primary HSC donor to be available when needed for the leukapheresis. In this respect the sponsor is also asked to clarify what the immune status of the donor should be with respect to the three targeted viruses;
- the extrapolation of the results obtained with products different from the one subject of this application
- the relative composition of the final products and the role of these two different lymphocyte populations in the therapeutic action of the product.

In addition the sponsor was invited to propose a different name that better describes the nature of the product

- 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 states that all recipients of HSCT could suffer from a viral infection during the course of one calendar year. However this seems to reflect the population at risk rather than the target group for treatment. The sponsor is therefore asked to provide an estimate of the target population of the treatment indication, based on existing data sources, and the definition of the population to be treated in relation to the specific condition (e.g. viremic and/or symptomatic population?).

In the written response, and during an oral explanation before the Committee on 3 September 2014, the sponsor elaborated on the characteristics of allogeneic stem cell transplantation, stressing that the donor derived immune system completely replaces the original recipient immune system. On that basis, it was discussed that the product is used to treat the donor immune system. The sponsor also discussed the envisioned therapeutic indication based on the clinical development, and described the constituents contained in the product. Moreover, the sponsor further elaborated on the prevalence calculations and on the basis for extrapolation from other products based on the immunological principles of the manufacturing process and the pre-clinical data.

The COMP considered that it would be difficult to consider medical plausibility based on data from a different product and not the one as proposed for designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 3 September 2014, prior to final opinion.

2.1.11 Product for treatment of Epstein-Barr Virus infections in patients following allogeneic stem cell transplantations-- EMA/OD/095/14
[COMP Co-ordinator: B. Dembowska-Bagińska]

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
  - the timing of administration of the proposed product, with particular attention to whether the use would be preventive or for treatment;
  - the feasibility of the intended clinical use of the product, linked to the need of the primary HSC donor to be available when needed for the leukapheresis. In this respect the sponsor is also asked to clarify what the immune status of the donor should be with respect to the three targeted viruses;
  - the extrapolation of the results obtained with products different from the one subject of this application
  - the relative composition of the final products and the role of these two different lymphocyte populations in the therapeutic action of the product.

  In addition the sponsor was invited to propose a different name that better describes the nature of the product

- 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 states that all recipients of HSCT could suffer from a viral infection during the course of one calendar year. However this seems to reflect the population at risk rather than the target group for treatment. The sponsor is therefore asked to provide an estimate of the target population of the treatment indication, based on existing data sources, and the definition of the population to be treated in relation to the specific condition (e.g. viremic and/or symptomatic population?)

In the written response, and during an oral explanation before the Committee on 3 September 2014, the sponsor elaborated on the characteristics of allogeneic stem cell transplantation, stressing that the donor derived immune system completely replaces the original recipient immune system. On that basis, it was discussed that the product is used to treat the donor immune system. The sponsor also discussed the envisioned therapeutic indication based on the clinical development, and described the constituents contained in the product. Moreover, the sponsor further elaborated on the prevalence calculations and on the basis for extrapolation from other products based on the immunological principles of the manufacturing process and the pre-clinical data

The COMP considered that it would be difficult to consider medical plausibility based on data from a different product and not the one as proposed for designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 3 September 2014, prior to final opinion.

2.1.12 Product for treatment of adenovirus infections in patients following allogeneic stem cell transplantations - EMA/OD/094/14
[COMP Co-ordinator: B. Dembowska-Bagińska]

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:

- the timing of administration of the proposed product, with particular attention to whether the use would be preventive or for treatment;
- the feasibility of the intended clinical use of the product, linked to the need of the primary HSC donor to be available when needed for the leukapheresis. In this respect the sponsor is also asked to clarify what the immune status of the donor should be with respect to the three targeted viruses;
- the extrapolation of the results obtained with products different from the one subject of this application
- the relative composition of the final products and the role of these two different lymphocyte populations in the therapeutic action of the product.

In addition the sponsor is invited to propose a different name that better describes the nature of the product

- 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 states that all recipients of HSCT could suffer from a viral infection during the course of one calendar year. However this seems to reflect the population at risk rather than the target group for treatment. The sponsor is therefore asked to provide an estimate of the target population of the treatment indication, based on existing data sources, and the definition of the population to be treated in relation to the specific condition (e.g. viremic and/or symptomatic population?).

In the written response, and during an oral explanation before the Committee on 3 September 2014, the sponsor elaborated on the characteristics of allogeneic stem cell transplantation, stressing that the donor derived immune system completely replaces the original recipient immune system. On that basis, it was discussed that the product is used to treat the donor immune system. The sponsor also discussed the envisioned therapeutic indication based on the clinical development, and described the constituents contained in the product. Moreover, the sponsor further elaborated on the prevalence calculations and on the basis for extrapolation from other products based on the immunological principles of the manufacturing process and the pre-clinical data

The COMP considered that it would be difficult to consider medical plausibility based on data from a different product and not the one as proposed for designation.

In communicating to the sponsor the outcome of the discussion, the sponsor formally withdrew the application for orphan designation, on 3 September 2014, prior to final opinion.

2.1.13 Cysteamine hydrochloride for treatment of cystinosis, Lucane Pharma SA - EMA/OD/106/14
[COMP Co-ordinator: B. Bloechl-Daum]

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

- Significant benefit

The sponsor is invited to state the stage of development of the product they are proposing namely the development of the sponsor's formulation of the ocular solution of cysteamine as it is acknowledged by the COMP that there is variability in the response to therapy due to the variability in the concentrations of cysteamine used in off-licence formulations prepared in the hospitals for patients with the condition.

In the written response, and during an oral explanation before the Committee on 3 September 2014, the sponsor clarified the source and production of the product they were seeking Orphan Designation for. There had been concerns from the COMP that the sponsor had no product. The sponsor indicated that they had a licencing agreement with a hospital pharmacy which had been producing the solution for over 25 years for patients who had the condition. As there was a product and the use of the product was well-established in France the basis of significant benefit was accepted.

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

The intention to treat the condition with the medicinal product containing cysteamine hydrochloride was considered justified based on bibliographical data in patients with the condition.

The condition is chronically debilitating and life-threatening, in particular due to progressive impairment of renal function leading to renal insufficiency and the development of ocular symptoms including loss of visual acuity, photophobia and keratopathy.

The condition was estimated to be affecting approximately 0.15 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 cysteamine hydrochloride may be of significant benefit to those affected by the condition. The sponsor has provided clinical data that demonstrate that the sponsor's product is effective in reducing corneal cysteine crystals in patients with the condition. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Cysteamine hydrochloride, for treatment of cystinosis, was adopted by consensus.

2.1.14 Recombinant human monoclonal antibody of the IgG1 kappa class against human macrophage colony-stimulating factor for treatment of pigmented villonodular synovitis, Novartis Europharm Limited - EMA/OD/107/14

[COMP Co-ordinator: A. Corrêa Nunes]

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:

- Condition

The sponsor should revise the proposed indication in accordance to the current WHO classification(A Review of the WHO Classification of Tumours of Soft Tissue and Bone An ESUN Book Review by Ghadah Al Saanna MD, Judith Bovée MD, PhD Jason Hornick MD, PhD and Alexander Lazar MD, PhD) to “treatment of tenosynovial giant cell tumour, localised and diffused type”.

- Seriousness

This section should be amended in light of the amended indication.

- Prevalence

This section should be amended in light of the amended indication.

In the written response, and during an oral explanation before the Committee on 3 September 2014, the sponsor submitted an updated scientific annex accepting the request of the COMP for a revised indication and also provided an updated seriousness section, as well as a prevalence calculation.

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

The intention to treat the condition with the medicinal product containing recombinant human monoclonal antibody of the IgG1 kappa class against human macrophage colony-stimulating factor was considered justified based on preliminary clinical data in patients affected by the condition who responded by reduction of tumour volume as assessed by imaging.

The condition is chronically debilitating due to the progressive course of the disease that results in the destruction of joints.

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 Recombinant human monoclonal antibody of the IgG1 kappa class against human macrophage colony-stimulating factor, for treatment of pigmented villonodular synovitis, was adopted by consensus.

2.1.15 Product for treatment of Merkel cell carcinoma - EMA/OD/079/14
[COMP Co-ordinator: B. Bloechl-Daum]

As agreed during the previous meeting, a list of issues was sent to the sponsor for response. The sponsor formally withdrew the application for orphan designation, on 15 August 2014, prior to responding to the list of issues.

2.2. For discussion / preparation for an opinion

2.2.1 (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one for treatment of Fragile X syndrome, Centre National de la Recherche Scientifique (CNRS) - EMA/OD/105/14
[COMP Co-ordinator: V. Stoyanova]

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

The intention to treat the condition with the medicinal product containing (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one (Chemical) was considered justified based on pre-clinical data using a valid model of the condition.

The condition is chronically debilitating due to developmental delay, severe neurobehavioral and neurocognitive complications.

The condition was estimated to be affecting approximately 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 (3S)-(+)-(5-chloro-2-methoxyphenyl)-1,3-dihydro-3-fluoro-6-(trifluoromethyl)-2H-indol-2-one, for treatment of Fragile X syndrome, was adopted by consensus.

2.2.2 Product for treatment of plasma cell myeloma - EMA/OD/087/14
[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 plasma cell myeloma, the sponsor should further elaborate on:

  - the results from pre-clinical studies, in particular the variability of responses in the different models and its relevance for the development of the product in 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 is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the ongoing clinical study to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication. In particular, the sponsor is asked to discuss patients' characteristics and prior treatments with regards to the duration of responses to the product.

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

2.2.3 Product for treatment of refractory and/or relapsed Richter's transformation - EMA/OD/078/14
[COMP Co-ordinator: J. Torrent-Farnell]

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

- Intention to diagnose, prevent or treat

The name of the condition should be justified as a distinct medical entity or a valid subset. The COMP considers that Richter's transformation is a stage of the broader condition Chronic Lymphocytic Leukaemia/lymphoma or DLBCL and would like the sponsor to further elaborate why they believe that it is a distinct condition. Note that this is 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).

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of refractory and/or relapsed Richter's transformation, the sponsor should further elaborate on:

  - the results obtained in the preliminary clinical study in patients with the chronic lymphoblastic lymphoma/leukaemia and patients with Richter's transformation.

- Number of people affected

As there is concern regarding the proposed condition Richter's transformation, the sponsor should consider recalculating the prevalence regarding the broader condition the COMP believes would correspond more accurately with the regulation.

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

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

- Significant benefit

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

The sponsor should detail the results of the Phase I clinical data they have to support the significant benefit assumption in the context of the current therapeutic management of patients.

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

2.2.4 Product for treatment of idiopathic pulmonary fibrosis - EMA/OD/130/14

[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 idiopathic pulmonary fibrosis, the sponsor should further elaborate on the relevance of the results of the bleomycin preclinical model taking into account the timing of administration of the product in relation to the bleomycin challenge.

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

2.2.5 Product for treatment of systemic sclerosis - EMA/OD/129/14

[COMP Co-ordinator: K. Westermark]

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 systemic sclerosis, the sponsor should further elaborate on:

  - the relevance of the results of the bleomycin study taking into account the timing of administration of the product in relation to the bleomycin challenge, and the relevance of the observations in preventing bleomycin-induced skin fibrosis for the proposed indication;
  - any further available data in either relevant models, e.g. the tight skin mouse model, or preliminary clinical settings, with the specific product as applied for designation.

- Significant benefit

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

In absence of any data supporting the medical plausibility of the product in treating the proposed condition the 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 October meeting.

2.2.6 Product for treatment of cystic fibrosis - EMA/OD/131/14

[COMP Co-ordinator: J. Eggenhofer]

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

In order to justify the plausibility of the proposed product the sponsor is invited to further elaborate on the data presented in this application and in particular:

  - the results of the in vitro chemotaxis assay where absolute values of neutrophil migration have not been provided;

- the clinical meaningfulness of the changes in the levels of sputum LTB4 in the phase I study, where LTB4 values showed a decrease at study day 9 and increased again after that time point;
- the relevance of the changes in serum CRP to the treatment of cystic fibrosis.

The sponsor is also invited to present quantitative results and figures from the two animal models presented to support of the medical plausibility of the proposed product.

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

2.2.7 Product for treatment of essential thrombocythemia - EMA/OD/124/14
[COMP Co-ordinator: M. Možina]

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

- Significant benefit

The Sponsor is requested to further discuss the arguments provided for significant benefit, in particular:

- to elaborate on how the results from the studies in healthy volunteers can justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication;
- it is not evident that the fewer adverse events seen in healthy volunteers will automatically translate into less adverse events in patients. The Sponsor is asked to comment on this and also discuss the severity and type of adverse events;
- the Sponsor should take into consideration more recent clinical data on Xagrid (publications) than the four mentioned studies used for the MAA and further elaborate on the significant benefit over authorised products.

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

2.2.8 Product for treatment of haemophilia A - EMA/OD/123/14
[COMP Co-ordinator: L. Gramstad]

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 haemophilia A, the sponsor should further elaborate on:

- the relevance of the preclinical model used for the treatment of haemophilia A, and the interpretation of the results obtained in the experiments;
- the reasons why haemophilic preclinical models have not been used.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential for improved efficacy in the condition, as well as improved safety versus authorised products. In addition, arguments are provided for improvement in patient care, since the product is intended for intradermal administration. The sponsor also mentions arguments that lie outside of the orphan framework, such as cost benefits, which cannot be considered and should not be further commented.

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

The comparison should be made on the basis of data and a comparative discussion versus the authorised products.

In addition, extrapolation from preclinical or early clinical studies cannot predict the safety of a product in its clinical setting, thus more relevant data is mandatory to justify safety arguments. The sponsor should further elaborate on the potential risks with the product and how this compares with the safety profile of current authorised medicinal products for the same condition.

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

2.2.9 Acamprosate calcium for treatment of fragile X syndrome, Real Regulatory Limited - EMA/OD/137/14
[COMP Co-ordinator: I. Bradinova]

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

The intention to treat the condition with the medicinal product containing acamprosate calcium was considered justified based on preclinical data and preliminary clinical data showing favourable effects on clinical aspects of the condition.

The condition is chronically debilitating due to developmental delay, severe neurobehavioural and neurocognitive complications.

The condition was estimated to be affecting 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 Acamprosate calcium, for treatment of fragile X syndrome, was adopted by consensus.

2.2.10 Adeno-associated viral vector serotype 8 containing the human *UGT1A1* gene for treatment of Crigler-Najjar syndrome, Généthon - EMA/OD/122/14
[COMP Co-ordinator: A. Corrêa Nunes]

The Committee agreed that the condition, Crigler-Najjar 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 8 containing the human *UGT1A1* gene was considered justified based on restoration of normal bilirubin concentrations in two preclinical models of the condition.

The condition is chronically debilitating due to the development of bilirubin encephalopathy (kernicterus), characterized by extrapyramidal dystonia, choreoathetosis, hearing loss due to auditory neuropathy and oculomotor paresis, and life-threatening with reduced life expectancy for type I patients.

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 exist 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 8 containing the human *UGT1A1* gene, for treatment of Crigler-Najjar syndrome, was adopted by consensus.

2.2.11 Product for treatment of erythropoietic protoporphyria - EMA/OD/127/14
[COMP Co-ordinator: L. Greene]

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 erythropoietic protoporphyria, the sponsor should further elaborate on:

  - the relevance of the ex vivo clinical model used for the treatment of erythropoietic protoporphyria, and the interpretation of the results obtained in the experiments within the context of the target patient population;
  - any pre-clinical in vivo data they may have in a relevant model of 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 October meeting.

2.2.12 Product for treatment of cleft lip and palate - EMA/OD/136/14
[COMP Co-ordinator: A. Magrelli]

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

- Intention to diagnose, prevent or treat

Cleft lip and palate should be justified as a distinct medical entity, or a valid subset of orofacial clefts. Note that this is 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).

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

  - any available data in either relevant models of the condition or preliminary clinical data in patients affected by the condition;

- the expected therapeutic benefit, in particular at what age the product would be administered and how this would fit into or affect the current standard of care.

- 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 has excluded part of the population affected by condition; the sponsor should re-calculate the prevalence estimate for the proposed orphan condition, or a valid subset, based on relevant epidemiological studies and registers using the correct epidemiologic indices.

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

2.2.13 Product for treatment of acute myeloid leukaemia - EMA/OD/103/14
[COMP Co-ordinator: B. Bloechl-Daum]

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

- Intention to diagnose, prevent or treat

The sponsor should further elaborate on the target condition and how the product directly treats it as it would appear that the product is specific for a treatment modality used in AML. This could imply a change in the condition. The COMP noted that the sponsor has an Orphan Designation for the prevention of Graft versus Host Disease and would like the sponsor to further elaborate on how this new proposed application does not overlap with the earlier designation.

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

- all the cell populations contained in the proposed product, and clarify as far as possible the role of each one of them in the assumed mechanism of action of the product in the settings of the proposed condition;
- why the product cannot also be used in non-haploidentical allogeneic HSCT;
- AML relapses and survival observed in the preliminary clinical studies vis a vis those outcomes that would be expected by the HSCT procedure alone;
- any available immune reconstitution endpoints in the preliminary clinical patients, in the context of HSCT;
- the available preliminary clinical studies in detail, including patient characteristics, endpoints studies and results in detail for the proposed condition as applied for designation.

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

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition. The sponsor should elaborate, based on data on the effects of the products versus non-ATIR treated standard of care, including HSCT alone.

In the absence of relevant data in the condition as applied for, significant benefit cannot be assessed at this time.

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

2.2.14 Glucagon for treatment of congenital hyperinsulinism, S-Cubed Limited - EMA/OD/128/14
[COMP Co-ordinator: K. Westermark]

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

The intention to treat the condition with the medicinal product containing glucagon was considered justified based on preclinical data and preliminary clinical data in healthy adults demonstrating that the product is capable of increasing blood glucose levels.

The condition is life-threatening due to death secondary to severe hypoglycaemia and chronically debilitating due to the neurological effects of chronic hypoglycaemia.

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 Glucagon, for treatment of congenital hyperinsulinism, was adopted by consensus.

2.2.15 Human recombinant bone morphogenetic protein 4 for treatment of glioma, STEMGEN S.p.A - EMA/OD/111/14
[COMP Co-ordinator: D. O'Connor]

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 human recombinant bone morphogenetic protein 4 was considered justified based on data from relevant preclinical models.

The condition is chronically debilitating, in particular due to compression and invasion of the surrounding brain structures leading to neurological deficits, and life-threatening with poor overall survival.

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 human recombinant bone morphogenetic protein 4 may be of significant benefit to

those affected by the condition. The sponsor has provided preclinical data showing inhibition of tumour volume progression and improved survival in relevant xenotransplantation models. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Human recombinant bone morphogenetic protein 4, for treatment of glioma, was adopted by consensus.

2.2.16 Product for treatment of systemic lupus erythematosus - EMA/OD/097/14
[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 systemic lupus erythematosus, the sponsor should further elaborate on:

  - the results obtained in vitro on the melanoma cell line in the treatment of systemic lupus erythematosus,
  - the relevance of the preclinical model used for the treatment of systemic lupus erythematosus, and the interpretation of the results obtained in the experiments.

- Number of people affected

The condition appears to have a higher prevalence than the one proposed by the sponsor and there are data in the public domain suggesting prevalence higher than the threshold of 5 in 10,000.

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

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

As it seems that the sponsor has excluded part of the population affected by condition; the sponsor should indicate on which population the prevalence calculation is based on.

- 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 should further elaborate on what the clinically relevant advantage is using data generated with the product in either pre-clinical in vivo models of the condition and/or preliminary clinical data in patients affected by the condition. Results should be discussed within the context of the current authorised medicines and standard of care.

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

2.2.17 Product for treatment of acute respiratory distress syndrome - EMA/OD/110/14
[COMP Co-ordinator: M. Možina]

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

- Number of people affected

The sponsor is invited to provide a sensitivity analysis of the estimated affected population including a worst case scenario, taking into account the change in classification that includes all ranges of severity including the cases previously classified as ALI.

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

2.2.18 Product for treatment of myotonic disorders - EMA/OD/074/14
[COMP Co-ordinator: D. O'Connor]

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

- Significant benefit

The sponsor has proposed that significant benefit is based on a major contribution to patient care.

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the current supply situation in Europe regarding the availability of authorised treatments for patients with myotonic disorders.

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

2.2.19 Nitric oxide for treatment of cystic fibrosis, PD Dr.med. Joachim Riethmüller - EMA/OD/036/14
[COMP Co-ordinator: J. Eggenhofer]

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

The intention to treat the condition with the medicinal product containing nitric oxide was considered justified based on preliminary clinical data showing reduction of bacterial load and improvement of lung function in patients affected by cystic fibrosis treated with the proposed product.

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

The condition was estimated to be affecting approximately 0.7 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 nitric oxide may be of significant benefit to those affected by the condition. The sponsor has provided early clinical data showing the large spectrum anti-infective activity of the product in patients affected by cystic fibrosis, accompanied by improvement of lung function. The mechanism of action of the product, targeting multiple functions of different types of infectious agents, carries the potential lack of development of resistances. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by cystic fibrosis.

A positive opinion for Nitric oxide, for treatment of cystic fibrosis, was adopted by consensus.

2.2.20 Product for treatment of acute peripheral arterial occlusion- EMA/OD/117/14
[COMP Co-ordinator: D. Krievins]

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

- Intention to treat

To establish correctly if there exists a scientific rationale for the development of the proposed product for treatment of acute peripheral arterial occlusion, the sponsor should further elaborate on the relevance of the preclinical studies and in particular:

- the clinical relevance of the methodology and results of the preclinical mesenterial artery study assessing reperfusion injury taking into account the different pathophysiology of the two conditions. The discussion should also include further elaboration on the dosage used to show an effect, which appears to be 10 fold higher than the assumed therapeutic dose, and efficacious only when used in addition to high doses of thrombolytic agents;
- the methodology and results of the experimental coronary artery occlusion/thrombolysis preclinical model in relation to the proposed condition;
- the relevance of reducing viscosity to the medical plausibility of using the product in acute peripheral arterial occlusion.

- Significant benefit

In order to establish the significant benefit of the proposed product the sponsor is invited to further discuss the potential advantage of the proposed product in relation to all possible current standards of care, including the combination of two or those, e.g. thrombolysis plus heparin, which is often the treatment of choice. Such discussion should be as much as possible supported by data.

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

2.2.21 Pyridoxal 5'-phosphate for treatment of pyridoxamine 5'-phosphate oxidase deficiency, Great Ormond Street Hospital for Children, NHS Foundation Trust - EMA/OD/104/14
[COMP Co-ordinator: V. Tillmann]

The Committee agreed that the condition, pyridoxamine 5'-phosphate oxidase deficiency, is a distinct medical entity and meets the criteria for orphan designation.

The intention to treat the condition with the medicinal product containing pyridoxal 5'-phosphate was considered justified based on preliminary clinical data in patients with the condition.

The condition is life-threatening due to intractable seizures which are rapidly fatal.

The condition was estimated to be affecting less than 0.02 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 Pyridoxal 5'-phosphate, for treatment of pyridoxamine 5'-phosphate oxidase deficiency was adopted by consensus.

2.2.22 Raxibacumab for treatment of inhalation anthrax disease, GlaxoSmithKline Trading Services Limited - EMA/OD/134/14
[COMP Co-ordinator: S. Thorsteinsson]

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

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

The condition is life-threatening due to development of pleural effusions, haemorrhagic mediastinitis and haemorrhagic meningitis linked to a fatality rate of 45 up to 100%.

The condition was estimated to be affecting less than 0.01 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 raxibacumab may be of significant benefit to those affected by the condition. The sponsor has provided preclinical data that demonstrate improved survival when the product was used in addition to levofloxacin, currently authorized for the treatment of the condition. The Committee considered that this constitutes a clinically relevant advantage for the patients affected by the condition.

A positive opinion for raxibacumab, for treatment of inhalation anthrax disease, was adopted by consensus.

2.2.23 Product for prevention of angioedema - EMA/OD/115/14
[COMP Co-ordinator: M. Možina]

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

- Intention to diagnose, prevent or treat

The sponsor should justify the exclusion of ACE-inhibitor induced angioedema based on international classification systems or underlying pathophysiology that renders this subset non-eligible for the proposed product. Note that this is for the purposes of orphan medicinal product designation; the sponsor's attention is drawn to the Orphan regulations and guidelines to clarify this (especially section A of ENTR/6283/00).

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

  - the relevance of the preclinical model used for the prevention of angioedema, and the interpretation of the results obtained in the experiments;
  - any further available data in either relevant models of the condition or preliminary clinical settings in patients affected by the condition;
  - why the proposed product would not work in ACE-inhibitor induced angioedema.

- 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".

As it seems that the sponsor has excluded a part of the population at risk of the condition, namely ACE-inhibitor-induced angioedema, the sponsor should re-calculate the prevalence estimate based on relevant epidemiological studies and registers for the proposed orphan condition.

- Significant benefit

The arguments on significant benefit are based on the new mechanism of action and the potential improved efficacy in the condition and a major contribution to patient care.

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

In the absence of any data of the product as proposed 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 October meeting.

2.2.24 Recombinant Human Insulin Receptor Monoclonal Antibody-Fused-α-L-Iduronidase for treatment of Mucopolysaccharidosis Type I, Voisin Consulting S.A.R.L. - EMA/OD/138/14
[COMP Co-ordinator: J. Torrent-Farnell]

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

The intention to treat the condition with the medicinal product containing recombinant Human Insulin Receptor Monoclonal Antibody-Fused-α-L-Iduronidase was considered justified based on preliminary in vivo pre-clinical data.

The condition is chronically debilitating and life threatening causing multi-organ disease, including skeletal deformities, developmental neurological delay followed by progressive deterioration, acute cardiomyopathy and obstructive airway disease.

The condition was estimated to be affecting approximately 0.03 in 10,000 persons in the European Union, at the time the application was made.

In addition, although satisfactory methods of treatment of the condition have been authorised in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing recombinant Human Insulin Receptor Monoclonal Antibody-Fused-α-L-Iduronidase may be of significant benefit to those affected by the condition. The sponsor has provided pre-clinical data that demonstrate a reduction of glycosaminoglycans in organs and tissues as well a reduction in brain lesions. The Committee considered that this constitutes a clinically relevant advantage.

A positive opinion for Recombinant Human Insulin Receptor Monoclonal Antibody-Fused-α-L-Iduronidase, for treatment of mucopolysaccharidosis type I, was adopted by consensus.

2.2.25 Recombinant human monoclonal IgG1 antibody for fibroblast growth factor 23 for treatment of X-linked hypophosphatemia, NDA Group AB - EMA/OD/133/14
[COMP Co-ordinator: V. Tillmann]

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

The intention to treat the condition with the medicinal product containing recombinant human monoclonal IgG1 antibody for fibroblast growth factor 23 was considered justified based on pre-clinical in vivo and clinical data in patients with the condition.

The condition is chronically debilitating due to inadequate mineralisation which results in soft bones and consequential bone deformities, and once the patients become weight bearing, it leads to the characteristic genu varum, genu valgum, tibial torsion, as well as rickets changes in metaphyses of the bones, especially notable in the wrists and knees on x-ray.

The condition was estimated to be affecting between 0.002 to 0.04 per 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 Recombinant human monoclonal IgG1 antibody for fibroblast growth factor 23, for treatment of X-linked hypophosphataemia, was adopted by consensus.

2.2.26 Product for treatment of post-polycythaemia vera myelofibrosis - EMA/OD/139/14
[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 post-polycythaemia vera myelofibrosis, the sponsor should further elaborate on the results obtained in the preliminary clinical study, by discussing the results obtained separately for primary, post PV, and post ET myelofibrosis patients.

- Significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preliminary clinical study specifically for PPVM, to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

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

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

2.2.27 Product for treatment of post-essential thrombocythaemia myelofibrosis - EMA/OD/116/14
[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 post-essential thrombocythaemia myelofibrosis, the sponsor should further elaborate on the results obtained in the preliminary clinical study, by discussing the results obtained separately for primary, post PV, and post ET myelofibrosis patients.

- Significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preliminary clinical study specifically for PETM, to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

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

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

2.2.28 Product for treatment of primary myelofibrosis - EMA/OD/140/14
[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 primary myelofibrosis, the sponsor should further elaborate on the results obtained in the preliminary clinical study, by discussing the results obtained separately for primary, post PV, and post ET myelofibrosis patients.

- Significant benefit

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

The sponsor is requested to further discuss the arguments provided for significant benefit and to elaborate on the results from the preliminary clinical study specifically for PMF, to justify the assumption of significant benefit over authorised medicinal products for the proposed orphan indication.

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

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

2.3. COMP opinions adopted via written procedure following previous meeting

2.3.1 [5-Amino-1-(4-fluoro-phenyl)-1H-pyrazol-4-yl]-[3-(2,3-dihydroxy-propoxy)-phenyl]-methanone for treatment of pancreatic cancer, Synovo GmbH - EMA/OD/085/14
[COMP Co-ordinator: B. Bloechl-Daum]

2.3.2 Recombinant human apolipoprotein A-I in a complex with phospholipids (CER-001) for treatment of ATP-Binding Cassette Transporter A1 (ABCA1) deficiency, Cerenis Therapeutics Holding SA - EMA/OD/063/14
[COMP Co-ordinator: F. Saleh]

2.3.3 Product for treatment of autosomal dominant polycystic kidney disease - EMA/OD/042/14
[COMP Co-ordinator: A. Corrêa Nunes]

2.3.4 Variant of recombinant human fibroblast growth factor 19 for treatment of primary biliary cirrhosis, Diamond BioPharm Limited - EMA/OD/101/14
[COMP Co-ordinator: A. Corrêa Nunes]

2.4. Appeal procedure

None.

2.5. Evaluation on-going

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

2.6. Validation on-going

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

3. Requests for protocol assistance

3.1 Product for treatment of glioma *[Coordinator: B. Bloechl-Daum]*

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

3.2 Product for treatment of Dravet syndrome *[Coordinator: K. Westermark]*

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

3.3 Product for treatment of congenital adrenal hyperplasia *[Coordinator: K. Westermark]*

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

3.4 Product for treatment of cytomegalovirus disease in patients with impaired cell mediated immunity *[Coordinator: B. Bloechl-Daum]*

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

4. Overview of applications

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

COMP co-ordinators were appointed for 20 applications submitted and 65 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 Imbruvica (1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H- pyrazolo [3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one); Janssen-Cilag International N.V.
[COMP Co-ordinator: B. Dembowska-Baginska]

a) for treatment of mantle cell lymphoma (EU/3/13/1115)

The COMP noted the CHMP opinion on MA adopted at the 21-24 July 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:

- Justification of significant benefit

The COMP invites the sponsor to provide additional justification on the issue of potential significant benefit over the authorised treatments, and in particular to provide additional clarifications on the clinically relevant advantage that ibrutinib may offer over the current standard of care in patients with relapsed/refractory CLL/SLL and relapsed/refractory MCL.

Clinical data generated with the product should be further elaborated in the relevant patient populations. A discussion of the open uncontrolled nature of the studies and the relevance of historical comparisons is also to be addressed.

b) for treatment of chronic lymphocytic leukaemia (EU/3/12/984)

The COMP noted the CHMP opinion on MA adopted at the 21-24 July 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:

- Prevalence

The sponsor should clarify if the proposed conclusion on the prevalence of CLL also includes the clinical presentation of SLL, and recalculate the proposed estimate for CLL/SLL also performing a sensitivity analysis on the assumptions used.

For the calculation and presentation of the prevalence data it is advised to refer to the "Points to Consider on the Calculation and Reporting of a Prevalence of a Condition for Orphan Designation" document available on the Agency website: (http://www.ema.europa.eu/pdfs/human/comp/043601.pdf)

- Justification of significant benefit

The COMP invites the sponsor to provide additional justification on the issue of potential significant benefit over the authorised treatments, and in particular to provide additional clarifications on the clinically relevant advantage that ibrutinib may offer over the current standard of care in patients with relapsed/refractory CLL/SLL and relapsed/refractory MCL.

Clinical data generated with the product should be further elaborated in the relevant patient populations. A discussion of the open uncontrolled nature of the studies and the relevance of historical comparisons is also to be addressed.

In its written response, and during an oral explanation before the Committee on 2 September 2014, the sponsor established a clinically relevant advantage was established in patients who had relapsed or refractory CLL and who had the 17pdeletion where an improvement in progression free survival over the comparator group was noted. This was considered the principle basis for a positive assessment regarding significant benefit. It was also noted that ibrutinib offered a major contribution to patient care as it is an capsule which is taken orally at home as compared to other approved therapies which are given intravenously to patients with these conditions in the hospital setting.

The COMP concluded that:

The proposed therapeutic indication:

> "IMBRUVICA is indicated for the treatment of adult patients with relapsed or refractory mantle cell lymphoma (MCL).
>
> IMBRUVICA is indicated for the treatment of adult patients with relapsed or refractory chronic lymphocytic leukaemia (CLL) /small lymphocytic lymphoma (SLL)"

falls entirely within the scope of the orphan indications of the designated Orphan Medicinal Product.

The prevalence of chronic lymphocytic leukaemia (hereinafter referred to as "the condition") was estimated to remain below 5 in 10,000 at the time of the review of the designation criteria and in particular to affect approximately 3 in 10,000 people in the EU.

The condition is life-threatening and chronically debilitating due to development cytopaenias (anaemia, neutropaenia, thrombocytopaenia), lymphadenopathy, splenomegaly, hepatomegaly and impaired production of normal immunoglobulin leading to increased susceptibility to infections.

Although satisfactory methods of treatment of the condition have been authorised in the European Union, the assumption that Imbruvica may be of potential significant benefit to those affected by the orphan condition still holds. This was based on a clinically relevant advantage due to an improved overall survival and progression free survival particularly in patients who had chromosome 17p deletion in chronic lymphocytic leukaemia. A major contribution to patient care was noted as it is an oral administration over current therapies which are intravenous and need to be administered in the hospital setting.

An opinion not recommending the removal of Imbruvica (1-[(3R)-3-[4-amino-3-(4-phenoxyphenyl)-1H- pyrazolo [3,4-d]pyrimidin-1-yl]-1-piperidinyl]-2-propen-1-one) (EU/3/13/1115 and EU/3/12/984) from the EC Register of Orphan Medicinal Products was adopted by consensus.

The draft public summaries of the COMP opinions were 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)

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

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

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

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

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

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

5.3.4 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)

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

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

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

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

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

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

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

5.3.12 Nintedanib for treatment of idiopathic pulmonary fibrosis; Boehringer Ingelheim International GmbH (EU/3/13/1123)

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

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

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

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

5.3.17 1-{3-[3-(4-chlorophenyl)propoxy]propyl}piperidine, hydrochloride for treatment of narcolepsy; Bioprojet (EU/3/07/459)

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

6. Procedural aspects

6.1 COMP Workplan 2015

A presentation was given on how the Committee workplan for the next years will be developed.

7. Any other business

7.1 EMA/RCE meeting: Methodology of clinical studies on rare cancers

Draft Agenda of the 3 October 2014 EMA/RCE meeting was circulated for information.

Date of next COMP meeting: 7-9 October 2014

List of participants

Chair:

Bruno Sepodes

Vice-Chair:

Lesley Greene	Patient representative for Eurordis

COMP Members:

André Lhoir	Belgium
Irena Bradinova	Bulgaria
Kateřina Kubáčková	Czech Republic
Jens Ersbøll	Denmark
Frauke Naumann-Winter	Germany
Geraldine O'Dea	Ireland
Nikolaos Sypsas	Greece
Josep Torrent Farnell	Spain
Annie Lorence	France
Adriana Andrić	Croatia
Sigurdur B. Thorsteinsson	Iceland
Armando Magrelli	Italy
Elena Kaisis	Cyprus
Dainis Krievins	Latvia
Aušra Matulevičienė	Lithuania
Henri Metz	Luxembourg
Judit Eggenhofer	Hungary
Albert Vincenti	Malta
Violeta Stoyanova-Beninska	The Netherlands
Lars Gramstad	Norway
Brigitte Blöchl-Daum	Austria
Bożenna Dembowska-Bagińska	Poland
Ana Corrêa-Nunes	Portugal
Flavia Saleh	Romania
Martin Možina	Slovenia
Zuzana Batová	Slovak Republic
Kerstin Westermark	Sweden
Daniel O'Connor	United Kingdom
Pauline Evers	Patient representative representing the European Genetic Alliances Network
Aikaterini Moraiti	Member nominated by the European Commission on the EMA's recommendation

Giuseppe Capovilla	Member nominated by the European Commission on the EMA's recommendation

Observers:

Virginie Hivert	Eurordis
Julian Isla	Dravet Syndrome Foundation